# INTERNATIONAL RECORD OF MEDICINE

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&

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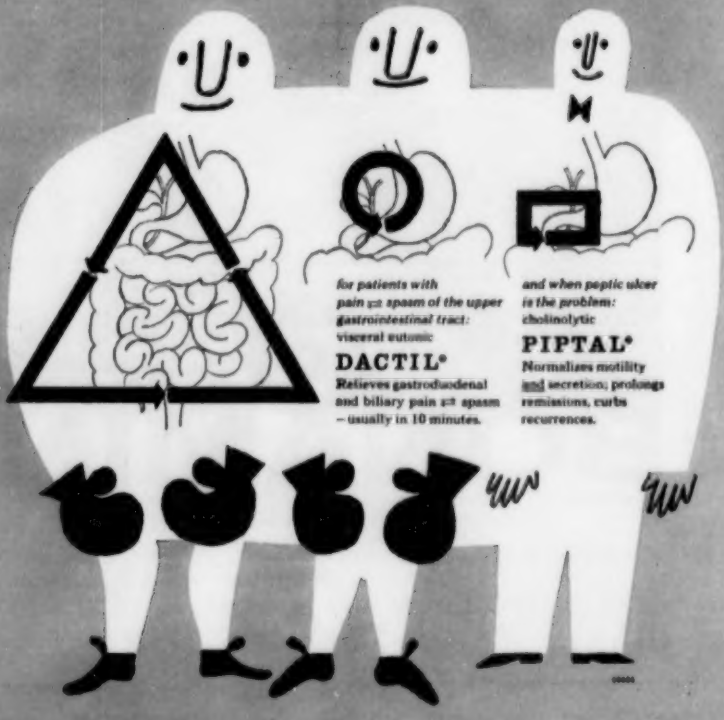

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# Hypertension: With a Review of Clinical Experiences with a *Rauwolfia* Preparation

*Henry L. Drezner, M.D.,* and Steven Horoschak, B.S.†*

## DEFINITION

A paucity of basic knowledge precludes an empiric definition for hypertension. Authoritative sources have given us such definitions as: (1) "An elevated blood pressure in man should be looked upon as a physical sign reflecting disordered function of the vascular system."[1] (2) "Hypertensive disease is not an entity, but a composite of a variety of diseases."[2] (3) "Essential hypertension is a morbid state in which fluctuating systolic and diastolic hypertension occurs."[3] (4) "Hypertension is a disease which may be the result of one or many biochemical lesions."[4]

It is difficult to form a correct judgment because of the fallaciousness of medical experiences. We should be impressed with the observation that "we are in a paradoxical situation, for even though we have more knowledge, we still have little clear understanding."[5] In the case of hypertensive disease it seems that more knowledge only adds to our ignorance. Probably we have been exposed to too many opinions and audacious conclusions to permit us to really distinguish fact from fiction.

## ETIOLOGY

Research on the etiologic factor or factors of hypertension has led to two theories: the neurogenic theory and the humoral theory.

The neurogenic theory suggests that strain of hard work and emotional tensions may influence the sympathetic nerves to increase the resistance of the peripheral circulation, causing the small vessels to become narrowed and thus elevating the blood pressure.

The humoral theory supposes the presence of an enzyme in the circulating blood stream that acts directly on the small vessels to reduce their lumen size.

Arteriolar constriction, a contributing factor in hypertension, may be the result of one or more biochemical imbalances.[4] Body endocrines or hormones are believed

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to occur in excess as a result of functional or nervous influences. In this respect, excessive adrenal cortical activity has been considered as a possible etiologic factor.[6]

Although much effort has been directed at determining the influence of the endocrine glands on the blood pressure, "there is no well-defined evidence that the adrenal gland is etiologically related to essential hypertension . . . neither is there sound evidence that other glands of internal secretion are in any way related to the cause of experimental or essential hypertension."[7]

The relationship of overweight to hypertension is emphasized in the observation, "the reduction of weight and the reduction of blood pressure in obese hypertensive patients often go hand in hand."[8]

Thus, "despite the prodigious literature and extensive research on the subject . . . the etiology, pathogenesis and clinical course are not known with certainty."[5]

## INCIDENCE

Although available statistics relating to the incidence of hypertension in the United States vary, there is complete agreement that hypertension is of enormous import as a cause of disability and one of the common causes of death. Approximately 15 million people in this country have an elevated blood pressure of some degree;[8] about 5 per cent of the adult population are hypertensive individuals.[9] The magnitude of the problem is manifested in the estimated dollars spent for antihypertensive drugs. The segment of the hypertensive population using antihypertensive drugs, on a basis of conservative estimations, spends 30 to 35 million dollars per year. Add to this the millions of dollars spent for research, and the amount would no doubt be adequate for us to retire and coddle our coronaries.

## SYMPTOMS AND DIAGNOSIS

Diagnosis frequently establishes a basis for therapeutics. The onset of hypertension may be observed in some patients as a result of changes in emotional tension. The neurogenic manifestations may be demonstrated by irritability, inability to relax, and changes in personality patterns.

Many persons with hypertension complain of headache, dizziness, shortness of breath, and changes in certain personality patterns. We must appreciate that it does *not* follow that blood pressure is always responsible for these symptoms. Headache is a very common symptom, but "it seems almost impossible for a patient who has been made aware of his blood pressure to remain free of this symptom because it is usually a product of anxiety."[11]

Whatever the basic cause of hypertension, as the disease progresses, the heart and vascular tree are more profoundly affected. Although it is thought that coronary disease is related to hypertensive disease, it was suggested, after a re-examination of this relationship, that "hypertension does not seem to be a factor responsible for coronary disease and occlusion in men, whereas it is a definite factor for their causation in women."[12]

It is quite apparent that the physician must exercise care and caution in evaluating the symptomatology. The patient and the disease should be considered of equal

importance. A searching personal and family history is a must; a thorough physical examination that includes measurements of pressure not only in the arms, but also in the legs, a close examination of the eye grounds, electrocardiogram and an estimate by roentgenogram of heart size, measurement of kidney function—all enter into making a diagnosis.

## TREATMENT

The treatment of hypertension is concerned with the lowering of the existing elevated blood pressure and the relief of the symptoms complained of by the patients.

Before treatment can be prescribed, there are certain criteria to be observed: (1) It is essential to study the patient thoroughly and to get to know him well. (2) Analyze the nature of his complaint. (3) Be aware of the capacities of the drugs to be used. (4) Initiate treatment with confidence at the proper time.

We will not review the general measures used in the management of the hypertensive patient. These measures are sedation, controlled physical and mental activities, dietary measures for overweight, and psychotherapy at the level of the family physician.

When we consider the drugs that have been and are available to meet the problem of hypertension from an etiologic standpoint, it must be admitted that "there is no adequate therapy of hypertension."[13] However, it has been suggested[14] that "excessive pessimism is not justified, because in many cases much can be done to alleviate symptoms and help the patient understand his problems."

The drugs enjoying popularity in the treatment of hypertension are the nitrates and nitrites, thiocyanates, hydralazine, *Veratrum viride* alkaloids, hexamethonium chloride, and *Rauwolfia serpentina*.

*The Nitrates and Nitrites*. These compounds have been used for many years, but this treatment is purely symptomatic. They presumably produce a relaxant effect on the musculature of the small vessels, causing peripheral vasodilation. These compounds, however, are weighted with disadvantages that include inconstant and transitory action and unpleasant side effects, such as severe headache and depression of renal activity. Patients also readily develop a tolerance to the drug, making it difficult to stabilize the dosage schedule. The consensus is that these compounds "are of no proved value."[15]

*Thiocyanates*. Sodium thiocyanate was first used in 1903 and the potassium thiocyanate was reintroduced for the treatment of hypertension in 1924.[16] Due to frequency of toxic reactions, they lost favor and were again pushed into the background. The suggestion was made[17] that these toxic effects could be adequately controlled by checking blood thiocyanate levels.

These drugs have attracted considerable attention because of their capacity to lower blood pressure. However, attention is called[18] to the wide variance in the individual tolerance and to the rate of renal excretion. It is also stated[19] that in some individuals "there is no margin of safety between the toxic and so-called therapeutically effective dose."

Thiocyanate is now believed to act in two ways: first, to cause cutaneous and mucosal phenomena characteristic of iodism; and second, to relax smooth muscles similarly to the nitrites.[20]

Therapeutic concentrations in the serum of patients have been observed to produce reactions such as increased nervousness, irritability, aches and cramps in the calf muscles, lethargy, and weakness of the arms and legs. Dermatologic reactions develop in some patients.

Toxic levels of thiocyanates may result in serious reactions such as nausea and vomiting, slurring of speech in older patients, followed by unsteady gait, disorientation, hallucination, mania, and delirium. It has happened that patients on thiocyanate treatment have been "picked up" as drunks, only to die.

The narrow margin of safety of these drugs, the contraindications, and the necessity of frequent blood level determinations should relegate them into an undesirable class for the management of hypertension.

*Hydralazine.* This is one of the newer compounds introduced for the treatment of hypertension. Its value is dependent upon several components of its pharmacologic action; the principal effect is central, apparently in the midbrain.

The action of this drug is heroic and results in side effects such as severe headache, palpitation, and tachycardia. Combinations of "weaker" hypotensive drugs with hydralazine have been suggested to modify its precipitous effect. In spite of this, side effects still occur.

*Veratrum viride. Veratrum viride* is not a new drug for the treatment of hypertension. Its use as a hypotensive drug was suggested in 1906, similar suggestions being made in 1914,[16] but it did not meet with success and the drug was "shelved."

*Veratrum* derivatives have recently been introduced and evaluated. It has been reported[21–23] that these derivatives "are not sympatholytic but have a central neurogenic vasodilator effect."

The variation in response to orally administered *Veratrum* derivatives is said to be related to a difference in absorption rates from the gastrointestinal tract into the blood or in rates of drug destruction or excretion.

These derivatives are effective orally as well as parenterally, but can cause nausea and vomiting at a dose very little, if any, higher than the hypotensive dose level.[24]

Patients on continuous chronic oral administration of the drug experience attacks of salivation, nausea, and vomiting, occasionally with collapse.

Tolerance seldom develops, but the patients' reactivity to the drug may increase. The many precautions attending the administration of these drugs make them impractical for general use.

*Hexamethonium Compounds.* These compounds, as ganglionic blocking agents, have an extremely profound hypotensive action and because of their capacities, represent potentially dangerous drugs. Not only do these compounds block the vasoconstrictor impulses in the sympathetic system, resulting in a profound fall in blood pressure, but they also block the ganglia of the parasympathetic system, producing varying degrees of paralysis of the ocular, gastrointestinal, and genitourinary musculature.

They induce a profound fall in blood pressure by blocking postural blood pressure reflexes resulting in postural hypotension.[25, 26] Reflexes controlling cardiac rate are depressed, and tachycardia may become a problem.[27]

Evaluating the clinical responses to oral hexamethonium therapy with regard to untoward side effects of the drug and the symptoms relieved, the following observa-

tions were recently reported: "Symptoms due to parasympathetic ganglionic block were anorexia, blurred vision, dry mouth, urinary retention, constipation, impotence, nausea, and vomiting. A curare-like symptom was fatigue. Diarrhea, abdominal cramps, dizziness, and syncope were seen when the blood pressure was reduced excessively or rapidly. These may be alarming and present differential diagnostic problems if one does not keep in mind that the patient has a systemic, parasympathetic block."[28]

We agree with the concept that "the hazards of these drugs are more impressive than the clinical benefits,"[24] and we subscribe to the view: "Disasters are probably inevitable in the early stages of experience with any new and potent drug, but the course of hypertension is so unpredictable, particularly in women, and the response to hexamethonium bromide has been so unreliable in our experience, that we do not propose to use these drugs again except in patients in whom a relatively early death appears inevitable with any other form of medical treatment."[29]

Drug therapy discussed thus far certainly is discouraging, and the question "What next?" may well be asked. With the exception of the nitrates and nitrites, the drugs discussed should be limited to continued clinical study and pharmacologic experimentation.

*Rauwolfia serpentina.* The most recent hypotensive drug to appear on this country's medical horizon is *Rauwolfia*. This drug was used in India before the Christian era, and the action of the drug most prized by the ancient healers was its sedative effect, obtained with large doses.

In 1942, the clinical effects of the drug in patients with essential and renal hypertension were reported.[30] Because of its effect, particularly on "the nervous symptoms of high blood pressure," its benefit was attributed to its action on the nervous system. The clinical use of the drug was intensified,[31–33] with the result of general agreement that the drug has hypotensive capacities of moderate potency, that it has a sedative effect, and that it slows pulse rate. It has been most successful in malignant hypertension.[34–36] The psychic effects of the drug, which include a sense of relaxed well-being, a decrease in irritability, and improvement in personality, were stressed.[33]

*Rauwolfia serpentina* was originally used as the powdered root of this shrub, but recently several alkaloids have been isolated from the extract of *Rauwolfia*. The alkaloids made available for clinical trial were the alseroxylon fraction and, more recently, the single alkaloid, reserpine.

It has been proved, clinically and in the laboratory, that the alseroxylon fraction possesses the total activity and all of the desirable therapeutic advantages of the whole root.[24, 37–39] This fraction apparently possesses a twofold action: it acts on the vasomotor center and on the cerebral centers.[24] It has been reported that it does not produce postural hypotension,[24, 34, 40–42] and in the usual dosage range it has neither adrenergic nor ganglionic blocking activity.[40, 42] No serious untoward side effects have been reported.[24, 28, 34, 37, 40] There may be a tendency for the patient to gain weight, usually as the result of relief of nervous tension.[33, 40] Tolerance apparently does not develop.[33, 34, 40]

Early in our investigation of *Rauwolfia serpentina* and two alkaloid derivatives, it

TABLE I

*Observations on 50 Patients Given Rau-Tabs*

| Number of patients | Degree of hypertension | Systolic and diastolic pressure | Remarks |
|---|---|---|---|
| 20 | Early mild benign | Systolic 150 to 200<br>Diastolic 100 to 110 | Majority showed normal readings at rest |
| 14 | Moderate benign | Systolic 200 to 240<br>Diastolic 110 to 120 | Rest helped lower pressure, but it did not reach normal |
| 10 | Late severe benign | Systolic 240 to 270<br>Diastolic 120 to 130 | Fluctuated under variable conditions |
| 6 | Elevated and fixed malignant | Systolic consistently over 240, diastolic over 140 | Pressures did not go below 220 at any time prior to treatment |

was decided to use the alseroxylon fraction as supplied in Rau-Tabs,* each tablet representing 2 mg. of the alkaloid. The patients were started on two tablets (4 mg.) in the morning and two tablets (4 mg.) at bedtime, based on the observation that very little additional hypotensive effect is produced by larger doses.

*Materials and Procedures.* The study involved 50 patients referred by eight physicians for medical and laboratory diagnostic procedures. They were sent back to their respective physicians with supplies of Rau-Tabs and recommendations of follow-up. These physicians reported back at regular intervals, giving their observations and impressions of progress in their respective patients.

In the 20 cases of early mild benign hypertension with an average diastolic pressure slightly over 100 mm. of mercury, on 8 mg. Rau-Tabs daily for four months, 85 per cent showed a decrease of an average of 13 mm. of mercury in diastolic pressure.

In the 14 cases of moderate benign hypertension with an average diastolic pressure slightly over 115 mm. of mercury, on 8 mg. Rau-Tabs daily for four months, 79 per cent showed a decrease of an average of 24 mm. in diastolic pressure.

In the 10 cases of severe benign hypertension with an average diastolic pressure of 125 mm. of mercury, on 8 mg. Rau-Tabs daily for six months, 90 per cent showed a decrease of an average of 33 mm. in diastolic pressure.

In the 6 cases of fixed malignant hypertension with an average diastolic pressure of 140 mm. of mercury, on 8 mg. Rau-Tabs, after eight months there was an average lowering of 37 mm. in diastolic pressure in 50 per cent of the cases, and control of associated symptoms in all of the patients.

We feel that the blood pressure should be reduced gradually and to that level at which the patient is comfortable. By this means the patient's body can adequately adjust itself to the changes.

The reports were largely in agreement that Rau-Tabs is an effective hypotensive drug, its effect being gradual and sustained. Most of the physicians reported that

* The trade name of National Drug Co. for the alseroxylon fraction of *Rauwolfia* is Rau-Tabs.

an appreciable effect was not observed for six or eight weeks in some of their patients, yet symptoms associated with their hypertensive state responded adequately. The patients experienced a tranquilizing effect, which may account for the rapid control of the associated symptoms. These observations confirm those previously reported—the drug has hypotensive capacities of moderate potency and has a tranquilizing sedative effect. Added to this is the consensus that it is safe and side effects are minimal compared with the crude root extract preparation and with the reserpine alkaloid.

It is unusual to get such unanimous agreement from a group of physicians, and it is this total agreement that impressed us. We are all well acquainted with the truism, "A drug that will be a good treatment for one man will be condemned as 'bad medicine' by another." This did not apply in this study in which eight physicians participated, each rendering his own observations and conclusions.

*Reserpine-Dimethylane.* We have stated that the onset of hypertension may be observed in some patients as a result of changes in emotional tension. The neurogenic manifestations may be demonstrated by irritability, inability to relax, and changes in personality patterns.

Case history surveys suggested a diagnosis of emotional hypertension in 15 patients with an average age of 32 years making up the group selected for this phase of our study. The blood pressure fluctuated with the stress situations faced by these patients.

Postulating that muscle relaxation and the control of the anxiety tension state in these patients would influence the hypertensive state, we started them on a compound, Dimethylane,* shown to possess these capacities. The procedure was standardized: one capsule, representing 0.25 Gm., after meals and at bedtime.

Although the associated symptoms, such as irritability, nervousness, and tension states, were adequately controlled within 10 days, the hypertensive state was not significantly stabilized.

We obtained Dimethylane, 250 mg., combined with reserpine, 0.25 mg., in enteric-coated capsules.† Two capsules were prescribed at bedtime for these patients. The hypertensive state in 86 per cent of the patients was brought to normal limits and stabilized within eight weeks. The remaining 14 per cent were continued on the treatment for as long as seven months without any side effects.

*Combinations of Antihypertensive Drugs.* Efforts have been made to combine in proper proportions the "dangerous" hypotensive drugs with *Rauwolfia*, with the idea of reducing their toxic effect and making use of their profound hypotensive capacities.

We would suggest that such combination treatment be limited to clinical study so that safety might be established. There is enough physician-patient anxiety in existence now without adding to it. The general practitioner, in addition to lowering the blood pressure and relieving symptoms, has another obligation—to prolong the life span of his patient. It is better to continue these treatments, which are safe, even though they be slow in their effect.

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* Dimethylane is marketed by National Drug Co.

† Dimethylane with reserpine was supplied through the courtesy of the Medical Research Department, National Drug Co.

COMMENT

The treatment of hypertensive disease states still continues on an empiric basis. As a result of our experiences with various drugs over a period of years, we have selected Rau-Tabs as a safe, slow-acting effective hypotensive drug. Judging from our limited experience with the combination, reserpine combined with Dimethylane has a potential of increased effectiveness.

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# The Artificial Uterus

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The artificial uterus is intended to replace the natural uterus when the latter expels an embryo prematurely at the fifth or fourth month of gestation or sooner. This often happens in such obstetric disorders as spontaneous or habitual abortion and eclamptic toxemia of pregnancy. In certain severe cases of Rh incompatibility, it might, in the future, conceivably be advisable actually to take the embryo from the mother and place it in the artificial uterus. After achieving further maturity in the artificial uterus, the young miscarriage would be transferred to an ordinary incubator and from there, eventually, to the crib.

This new organ complex, the artificial uterus, is dependent upon two other artificial organs, namely, the artificial kidney and the artificial heart-lung. The artificial uterus also depends upon the integrity of the embryo, umbilical cord, and placenta as one unit. The umbilical cord is not cut and the embryo is not separated from the placenta; this is the crux of the thesis of the artificial uterus.

The combination of a highly advanced type of incubator plus the new concept of the *fetus-cord-placenta* as one unit, utilizing a circulating blood stream that is constantly being oxygenated, purified, and nourished, constitutes the artificial uterus—what is hoped will become a salvager of miscarriages and abortions.

The placenta, or afterbirth, which is made up of tissue from both mother and embryo, is an organ that permits the mutual exchange of blood components; in the artificial uterus, as in the natural womb of the mother, the maternal blood and the fetal blood do not mix.

At first it was thought that the umbilical cord would shrivel up outside of the uterus. However, a segment of umbilical cord was placed in normal saline in a glass vial and remained perfectly intact, clear, and glistening for more than six months.

In addition, to prove the ability to transport nutrients and waste products through and from its vessels, the following experiment was performed. It demonstrates the ability of the placenta and umbilical cord system to permit ionic absorption and transfer to the embryo extra utero.

White rats were cesareanized on the seventeenth day of gestation under intraperitoneal barbiturate anesthesia. The embryos were delivered by hysterotomy, the surgeon being careful not to injure the umbilical cord and placenta attachment. The placentas were immersed in a lake of radioactive sodium in a watch glass for five minutes. The placentas and cords were then cut off and the embryos exposed to the Geiger counter. An appreciable amount of radioactivity was demonstrated to be present in the fetus.

The extrauterine passage of sodium ions through the placental capillaries and the umbilical vein to the body of the fetus demonstrates one of the component mechanisms upon which the function of the artificial uterus depends.

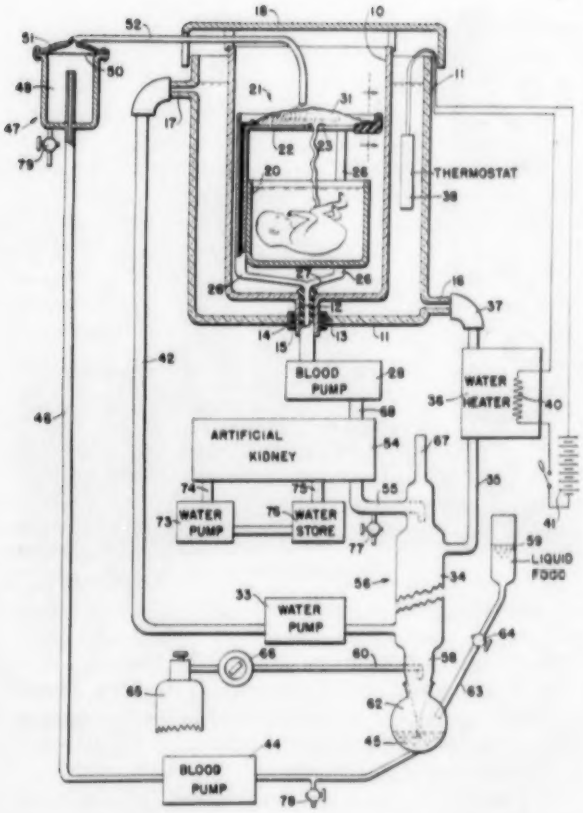


FIG. 1. Diagrammatic illustration of the artificial uterus.

What are the fetal requirements that should be supplied by the artificial uterus?

1. Continuous flow of blood to and from the fetus.
2. Blood carrying nutrients and oxygen and removing carbon dioxide and waste products.
3. Even temperature (simulating intrauterine temperature).
4. Relative freedom from environmental shock injury.
5. Expansible chamber or a chamber large enough to accommodate a full term child.
6. Bacteriologic sterility.

The artificial uterus that answers these requirements (fig. 1) is an advanced type of incubator designed to salvage the fetus prematurely passed as a "miscarriage" by the mother prior to the age of viability. The fetus may also be taken from the mother by cesarean section in certain cases of Rh incompatibility, of eclampsia (if removal of the fetus is indicated before the period of viability), and in cases of threatened abortion if there is a history of habitual abortion or of sterility. The

FIG. 2. Model of the artificial uterus (without the artificial kidney).

artificial uterus attempts to imitate the natural uterus in the following ways:

1. The umbilical cord is not severed; the baby, placenta, and umbilical cord are considered as one unit and are removed by cesarean section. When delivery has taken place from below, rapid manual removal of the placenta without severing the cord is recommended if possible.

2. The baby is placed in a fluid medium chemically and physically simulating the amniotic fluid.

3. The "uterus" is expansible or large enough to accommodate an embryo that would increase in size.

4. The "uterus" is uniformly heated.

5. The placenta is placed in a blood chamber and its cotyledons are bathed in blood just as truly as if they were in the maternal sinusoids. The maternal blood from the uterus enters the intervillous space through a central arterial sac; there are only a few such sacs per cotyledon.

The pressure of the blood ejected from the terminal sacs is about 40 mm. of mercury and the blood is sprayed from the terminal sac through the intervillous space toward the fetal surface like water from the end of a fire hose.

The fetal blood and maternal blood actually do not mix.

As Arey[2] states, "The blood of the mother and that of the fetus circulate in totally independent and separate channels. The relation of the chorionic villi and its vessels to the maternal blood which bathes the villi is much like that of the blood vessels of the hand to the water in a tub when the arm is immersed. A more precise

comparison is furnished by the intestinal villi and the fluid content of the gut cavity during digestion. In the case of both chorionic and intestinal villi there is no direct contact or mixture between the external fluid and the blood of the villus, but their only communication is through diffusive interchange."

6. The placental blood chamber is connected to an artificial kidney and an artificial heart-lung, thereby bringing nutrient material and oxygen to the placenta and affording a means of waste product excretion. The placental blood chamber may instead be connected with the blood system of the embryo's own mother by connection with an artery and vein of the mother.

7. Employment of aseptic technique and the use of antibiotics.

The artificial uterus would be transparent, so that the development of the fetus could be observed from day to day. An electrically conductive, transparent "glass skin" could be applied to the outside to maintain the desired level of heat. Experimentation in the use of the artificial uterus will emphasize the normal but nonviable fetus in the 200 to 450 Gm. range.

The perfection of the artificial kidney and the artificial heart-lung is patiently awaited, for upon these will the success of the artificial uterus so much depend.

The artificial uterus thus comprises a synthesis of two artificial organ mechanisms —plus the new concept of fetus-cord-placenta integration into one unit in direct imitation of the natural state.

This is based on the belief that the young fetus is not ready to use its lungs, heart, or digestive tract and must depend upon its own placenta and umbilical cord for nutrient sustenance and gaseous interchange. Direct cannulization of the umbilical artery and vein may make it possible to by-pass the placenta, although in early embryos with correspondingly young and feeble hearts, it would seem logical to retain the placenta, thus imitating as much of the natural state as possible.

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# The Response of Patients with Uremic Coma to Adenosine-5-Monophosphate

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Although the term "uremia," designating renal insufficiency, is firmly established in medical literature, it is in truth a misnomer. The symptoms of uremia do not correspond to the degree of retention of the nitrogenous end products, such as urea or creatinine. This is especially true with regard to the coma of uremia, which is perhaps its most serious symptom and which may occur at almost any level of nitrogenous retention.

Whatever the actual cause of uremic coma may be, in the final analysis there must be a reduction in the level of high energy phosphate bonds in the cerebral tissue for the patient to be in coma. In this preliminary study, we attempted to increase the high energy phosphate bonds (adenosine triphosphate, ATP) by supplying a precursor, adenosine-5-monophosphate‡($A_5MP$). The production of high energy phosphate bonds normally occurs in the metabolism of carbohydrate by cerebral and other tissue, and these reactions produce the energy that is used in the function of the nervous system and other tissues.

With the possible exception of glutamic acid, glucose is the only substance metabolized by brain tissue.[1] The end result of this metabolic activity is the production of ATP, which supplies the energy necessary for the proper function of nerve and other tissues. Presumably, in coma there is a short supply of this substance in the brain tissue.

We treated 3 patients with uremic coma of varying duration. All the patients finally died of irremediable conditions, which in 2 of the cases were urologic lesions that could no longer be treated surgically with safety to the patient. However, in each case the patient was roused from coma by $A_5MP$. In one patient, 1 ml. (20 mg.) of the aqueous solution was given every hour for five doses for two days, and then 1 ml. of 100 mg. of $A_5MP$ in gelatin was given daily. In another patient, 2 ml. of $A_5MP$ gel (100 mg./ml.) was given the first day and 1 ml. thereafter. In the third patient, 1 ml. of $A_5MP$ gel (100 mg.) was given twice daily. Since this is a preliminary study, different modes of treatment were tried in each patient. We plan now to use the following method: 1 ml. of aqueous $A_5MP$ (20 mg./ml.) every hour for five doses the first day, and then 1 ml. of $A_5MP$ gel (100 mg./ml.) daily thereafter.

It has been shown by Albaum et al[2] that injection of $A_5MP$ increases the blood

Thanks are due to Dr. Edward K. Harvill of the Bischoff Division, Ames Co., Inc., for generous supplies of adenosine-5-monophosphate used in this study.

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‡ The trade name of the Ames Co., Inc., for adenosine-5-monophosphate is *My-B-Den* (in aqueous and gel forms).

levels of ATP. Albaum et al[3] also demonstrated that $A_5MP$ injected into the rat causes a statistically significant increase of ATP and phosphocreatine in both muscle and brain, without, however, an increase in total purine. Albaum considered this to be due to a shift in components of the nucleotide pool.

In this article, we are concerned specifically with treatment of coma in these patients on a physiologic basis. However, the patients must still be treated in the conventional manner, with due consideration for fluid and electrolyte balance and anemia. We are merely adding a drug that we believe may be useful in the therapy of these patients. If the patient is conscious and can be fed by mouth, his care can be simplified to a remarkable degree.

## CASE REPORTS

*Case 1.* The patient, H. L., was a 60 year old man admitted December 21, 1953 with a history of bilateral kidney disease and in coma. One kidney was thought to be hydronephrotic and the other was said to contain stones. Physical examination revealed a comatose patient, with slight cyanosis, who was thrashing around in bed. His pupils did not react and were dilated, and the eye grounds showed thickened arteries and patches of exudate. The heart was enlarged. Blood pressure was 200/100 mm. of mercury. The abdominal examination was negative. Knee jerks were elicited and bilateral Babinski reflexes were present. The rectal examination was negative. There was right facial weakness. Impression after physical examination was of uremia and possible cerebral vascular accident. On the following day a definite right-sided hemiplegia was noted.

Telephone consultation with the previous physician revealed that treatment of this patient had been started two years previously. An intravenous pyelogram showed no secretion in the right kidney and multiple stones in the left kidney. The patient's blood pressure was 220 to 240 mm. of mercury systolic. During this time he had several episodes of severe hematuria. The bladder urine often contained almost pure pus. This was helped by oxytetracycline* and bladder irrigation. Blood findings on admission were: urea nitrogen, 154.0 mg./100 ml.; creatinine, 13.8 mg./100 ml.; sugar, 167.0 mg./100 ml.; carbon dioxide combining power, 28 vol./100 ml.; calcium, 12.0 mg./100 ml.; and phosphorus, 7.95 mg./100 ml.

Attempts were first made to see if the blood pressure could be lowered. Bistrum, in 0.5 ml. dosage, was given every three hours. To combat the acidosis, 1000 ml. of Ringer's lactate solution was given. Digitaline Nativelle, 1 ampule, was given daily. Because of severe anemia (7.6 Gm. hemoglobin and 2,000,000 red blood cells/cu. mm.), the patient was also given a transfusion of 250 ml. of blood each day for four days. The urine on admission showed 4 plus albumin, a few white blood cells, and numerous bacteria.

The patient was seen on December 22, 1953, by a consulting urologist, who found a right hemiplegia, left pyonephrolithiasis with a nonfunctioning right kidney, and acidosis. A culture of the urine was recommended, and specific antibiotics, depend-

* The trade name of Chas. Pfizer & Co. for oxytetracycline is Terramycin.

ing on the culture, were given. The culture revealed *Staphylococcus albus*, sensitive to oxytetracycline.

On January 1, 1954, the patient developed myocardial failure, whereupon he was digitalized and given oxygen. The heart failure was rapidly brought under control. On January 10, he was re-evaluated; he was then still in coma. The urea nitrogen on December 26, 1953, was 134.0 mg./100 ml. and on December 27 it was 120.0; on December 30 it was 95.2; on Jan. 4, 1954, 116.0; on January 7, 103.0; and on January 9, 89.0 mg./100 ml. of blood. In spite of the fluctuations of the urea nitrogen in the blood, the patient was still in coma and responded only slightly to very strong stimuli.

On the basis described in detail later in this article, he was given $A_5MP$ intramuscularly, 20 mg. every hour for five hours. This was to supply the ATP necessary for brain function. After the fifth dose, he became partially conscious. The dosage was repeated the following day. From January 12, he was given $A_5MP$ gel, 100 mg./day. He was aroused from coma and was not again in coma until he died.

On January 15, when it was found that oxytetracycline was no longer effective in inhibiting the growth of organisms in the urine, erythromycin* was substituted; the organisms were still sensitive to this antibiotic. On January 31 it was found that erythromycin was no longer effective in inhibiting the culture of the organisms, so thiasulfil was tried. From January 13, the patient was out of bed and on a high fat, low protein diet. He did not receive any intravenous feedings after that date.

The patient did fairly satisfactorily until February 15, 1954. His urea nitrogen level had receded to about 50 mg./100 ml. and his creatinine level to 4.2 mg./100 ml. However, it was a foregone conclusion that he would not continue to do well, because no definitive therapy was given. On February 5, 1954, an intravenous pyelogram showed that neither kidney secreted any dye and that the left kidney was larger than normal and contained numerous calcific shadows. The urologist did not feel it was wise to operate.

On February 15 the patient had a sudden onset of dyspnea and expectorated a small amount of blood. Examination revealed râles at the base of the right lung up to the scapula, with dullness over the area. A roentgen-ray examination revealed consolidation of the right lung and scattered infiltration of the left lung. The diagnosis was considered to be confluent bronchopneumonia. There was no evidence of peripheral thrombosis.

From this point on, the patient did poorly in spite of all the antibiotics. On February 22 a friction rub was heard over the precordium. The urea nitrogen was 74.0 mg./100 ml., rising at death to 109.0 mg./100 ml. For several days he was moribund, and on March 16 he died in pulmonary edema.

The remarkable thing about this patient is that from the time $A_5MP$ was started until several days before his death, he was not in coma. Apparently we have a substance that supplies the high energy phosphate bonds to allow the brain to function, even though the ultimate outcome is poor.

*Case 2.* L. S., a 68 year old woman, was admitted on June 8, 1954, and died on

* The trade name of Eli Lilly Co. for erythromycin is Ilotycin.

June 17. The patient was admitted critically ill, in a deep coma. She had been a known diabetic for many years, taking 25 units of protamine zinc insulin daily. She also had a severe form of parkinsonism. On the morning of admission, the patient's daughter found that the patient could not be aroused and noted a flapping of the right side of her face.

Physical examination revealed a comatose patient with a temperature of 105 F. The heart was enlarged, the rate regular, and the blood pressure 180/100 mm. of mercury. Examination of the lungs revealed râles in both bases. The extremities showed rigidity and tremor, with a right Babinski sign, spontaneously and after challenge. There was also weakness of the right lower extremity. The impression was that the patient was in diabetic coma, had sustained a cerebral vascular accident, and had bronchopneumonia as well.

Blood chemistry findings on the day of admission showed urea nitrogen of 59.0 mg./ml., blood sugar of 620 mg./100 ml., and a carbon dioxide combining power of 44 vol./100 ml. The urine showed a specific gravity of 1.031, with a trace of albumin, 4 plus sugar, and a trace of acetone.

Considering the blood chemistry findings, it was felt that uremia was also involved in causing the coma. On the first day the patient was given 200 mg. of $A_5MP$ in gel to see if consciousness could be restored. On examination on June 9, the patient was conscious. She was given large quantities of insulin and placed on a four hour urine test schedule with insulin to cover the amount of sugar passed. It was found, however, that this was an inaccurate method in the case of this patient because of a high kidney threshold. However, at no time did this patient show a carbon dioxide combining power of less than 38 vol./100 ml. and usually the figure was 44 vol./100 ml. We therefore felt that the diabetes was not the significant factor producing this patient's coma.

On June 10 the patient was conscious; the following day she was conscious enough to swallow fluid and was able to recognize her daughter. On June 12 her condition was critical, although she was conscious. There were râles in several areas of both lungs. Her temperature continued to range from 102 to 100 F. even though full doses of antibiotics were given. Urea nitrogen figures were: June 8, 59.0; June 9, 81.6; June 10, 102.0; June 11, 96.0; June 12, 67.0; June 14, 96.0; June 15, 104.0 mg./100 ml. The blood sugar remained elevated in spite of massive amounts of insulin, but before death the level fell to 360 mg./100 ml. of blood. From June 13 until June 16, when the patient died, she was in shock, with a systolic blood pressure level around 60 mm. of mercury. On the day of her death it was found that both heels had become gangrenous.

In summary, this patient was admitted in coma, to which probably the diabetes, cerebral vascular accident, and, especially, uremia contributed. We feel that the diabetes contributed the least, since only occasionally did the urine show more than a trace of acetone and the carbon dioxide combining power was always near the normal range. $A_5MP$ contributed in keeping this patient conscious until the inevitable end. It was given daily from June 8 to June 13, after which time it was felt that it would serve no purpose.

*Case* 3. A. L., a man aged 61 years, was admitted to the hospital on April 13,

1954, in a state of coma. This patient was known to have a bilateral hydronephrosis secondary to a hypertrophied prostate that had never been surgically corrected. Instead, he had had a permanent cystotomy performed three years before the present admission. Severe anemia necessitated repeated blood transfusions. In the two months previous to admission, acidosis had been noted, with retention of phosphates, sulfates, and urea nitrogen, and decreased blood calcium. In the preceding week, persistent hematuria was present, caused by an impacted ureteral stone.

On the evening of admission, the patient collapsed and went into coma, with Kussmaul's breathing and repeated generalized convulsions. Blood pressure was 180/116 mm. of mercury; the carbon dioxide combining power was 16 vol./100 ml. The blood count, after the patient received 1000 ml. of whole blood on the same day, was: red blood cells, 3,500,000 per cu. mm.; hemoglobin, 8.9 per cent; white blood cells, 7850 per cu. mm.; polymorphonuclear leukocytes, 82 per cent; lymphocytes, 15 per cent; and monocytes, 3 per cent. The urea nitrogen was 150 mg.; creatinine, 20 mg.; and glucose, 201 mg./100 ml. The patient was given an infusion of saline and 4 per cent sodium bicarbonate, with a rise in carbon dioxide combining power to 28 vol./100 ml. in four hours. The electrocardiogram revealed evidence of hyperpotassemia.

The patient was in a severely stuporous, unresponsive state and could not be aroused except with the greatest difficulty. On April 15 the carbon dioxide combining power was 27 vol./100 ml. Adenosine-5-monophosphate gel, 100 mg., was given intramuscularly twice daily to see if it would improve the patient's stupor, although no lasting improvement in his general condition was anticipated. Within four hours after the first injection, the patient was able to recognize his wife and daughter and answer questions quite rationally, and he seemed generally improved. This observation was also made by the family physician and the nurse in attendance. The next day the patient seemed brighter, generally improved, and definitely more comfortable. On that day the carbon dioxide combining power was 35.8 vol./100 ml., although hematuria persisted. Parenteral glucose, sodium lactate, saline, vitamins, and antibiotics were constantly administered. On April 16 the patient was still alert and was able to swallow fluids. Toward the evening of the same day, he again suffered convulsive seizures and began Cheyne-Stokes respiration. Adenosine-5-monophosphate administration was discontinued. Progressive deterioration followed the next day, with deepening coma and hyperthermia, and the patient died after a convulsive seizure.

## DISCUSSION

In uremic coma, there is an accumulation of protein end products in the blood, as well as disturbances in water and electrolytes. There is no correlation between the protein end product level in the blood and the cerebral symptoms. Dialysis with the artificial kidney may, in some instances, reverse uremic coma, but it may also remove an inhibitor of cerebral enzyme activity, as well as the protein end product, i.e., urea nitrogen or creatinine. Removal of the enzyme inhibitor would allow the cerebral metabolism to continue. The specific enzyme inhibitors are unknown. Studies of the cerebral metabolism of patients in uremic coma show good vascular

delivery to the brain and an adequate substrate (glucose) supply but a depressed cerebral metabolic rate.[1] This combination of facts would indicate a blocking of an essential enzyme in the metabolism of the brain cells.

We have attempted in this work to circumvent the specific enzymatic disturbance by supplying a substance, adenosine-5-monophosphate ($A_5MP$), that can directly increase the high energy phosphate bonds so that nerve cells are able to perform the necessary functions. Thus, we may be able to arouse a patient out of coma, even if we cannot remove the specific enzyme inhibitors. Of course, reversal of the coma will be only temporary if the underlying defect cannot be corrected.

To understand the rationale of our method of treatment, it is necessary to review cerebral metabolism. The brain cells require energy to perform their various functions. The substrate (the substance that the cells use as food) combines with oxygen in the presence of enzymes or catalysts, and these reactions yield energy in the form of high energy phosphate bonds (adenosine triphosphate or ATP). Any disturbance of the substrate supply, oxygen supply, or enzyme activity of the brain cells will result in impaired function of the brain.[1] The more severe forms of impaired function result in coma.

The brain and nervous system obtain energy principally from glucose, although under certain circumstances glutamic acid may also act as a substrate. It will be shown that ATP enters into the glucose metabolic cycle several times in the scheme. Since Albaum[2] has shown that injected adenosine-5-monophosphate ($A_5MP$) causes a fourfold increase in the ATP levels in the blood, it can be seen that $A_5MP$ is also an important metabolite in the intermediate metabolism of glucose.

The initial metabolic step in carbohydrate metabolism is the phosphorylation of glucose to form glucose-6-phosphate, the phosphate donor being ATP. The reaction is catalyzed by hexokinase. Glucose-6-phosphate can be converted into glucogen in the liver and muscles or to glucose in the liver, or it can be degraded to pyruvic acid anaerobically through a series of reactions called glycolysis (Embden-Meyerhof cycle, fig. 1).

In the absence of oxygen, pyruvic acid is transformed into lactic acid, but in the presence of oxygen, a series of reactions occurs that is called the tricarboxylic acid cycle of Krebs. Pyruvic acid is converted to acetyl-Co-A, which by condensation with oxalacetate forms citrate, the first intermediate in the Krebs cycle. In the course of conversion again to oxalacetate, the equivalent of 1 molecule of acetic acid is oxidized, with the production of a large amount of energy in the form of high energy phosphate bonds, i.e., ATP. The various steps of the Krebs cycle include the formation of cis-acomitate, iso-citrate, fumarate, and malate. Various enzymes or coenzymes are required to catalyze these reactions, and interference with their activity, either by specific inhibitors or by lack of activators, will impair glucose metabolism.[1] This will result in decreased energy formation and altered activity of the brain and nerve cells (fig. 1).

It might seem at first glance that barbiturate coma has nothing whatever to do with uremic coma, yet in both these states ATP levels in the brain are apparently at a low point. We have a few observations on barbiturate coma that are interesting in this regard.

The exact site of action of barbiturates on the cerebral metabolism in the production of coma is unknown. The depression of the cerebral metabolic rate in barbiturate narcosis is not in proportion to the functional depression; i.e., depression of consciousness is usually very severe before the cerebral metabolic rate is even demonstrably depressed.[1] The situation is similar with relation to alcohol. One of the explanations for this curious phenomenon is given by Bain,[4] who postulates that in those instances in which oxidation is normal, the functional depression of the nervous system may be due to the dissociation or uncoupling of the process of formation of high energy phosphate bonds from oxidation. As we noted before, these reactions usually go together. Thus, ATP formation in the instance described may be entirely inhibited even while oxidation proceeds quite satisfactorily. If ATP formation is stopped, cerebral activity cannot go on and coma results. Thus, $A_5MP$, by producing sufficient ATP for cerebral functioning, may rouse the patient out of coma, and multiple doses may keep him out of coma until the barbiturate can be excreted or destroyed. We have had no experience as yet with the use of $A_5MP$ in barbiturate poisoning as such.

However, we have two observations that suggest the effect of $A_5MP$ on barbiturate toxicity. A 70 year old woman took 1.5 gr. of Seconal to make her sleep, but sleep was not induced. One capsule after another was taken, until six or more were consumed; the exact number was unknown, but at least six were taken. The total,

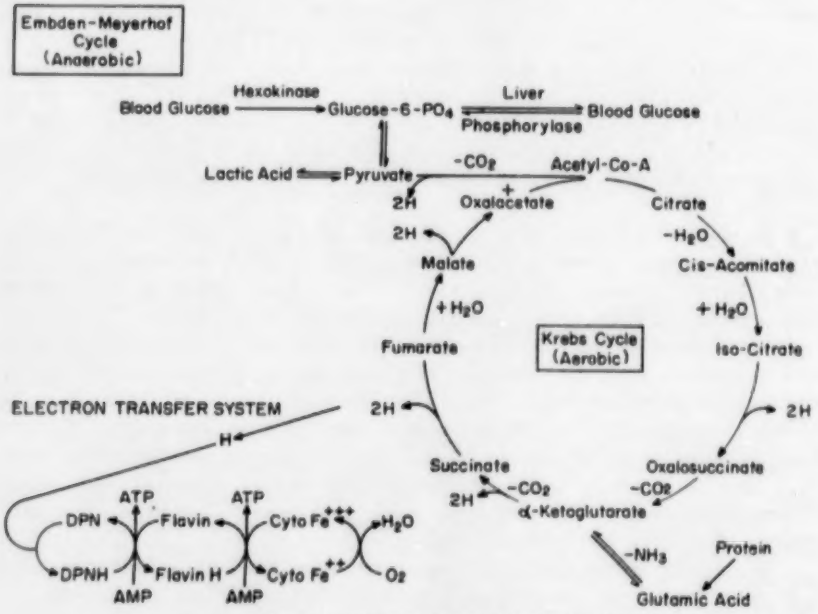


FIG. 1. The anaerobic and aerobic metabolism of glucose by cerebral cells.
Adapted from the *American Journal of Medicine* 15:806, 1953. Reproduced by permission.

9 gr., certainly is not a toxic dose, but the patient could not be roused. Aqueous $A_8MP$, 20 mg., and 100 mg. of $A_8MP$ were given intramuscularly. In a half hour, the patient was awake and alert, and was answering questions freely.

Another patient in the hospital appeared to have an exaggerated reaction to a barbiturate after a pleural tap. She had carcinoma of the breast with pleural and lung metastasis. Seconal (1.5 gr.) narcotized her so that she could be roused only with great difficulty. Undoubtedly, her poor general condition contributed to the depth of narcosis with this small dose; 20 mg. of aqueous $A_8MP$ intramuscularly aroused her completely in one-half hour.

Animal work seems to bear out these impressions. Langlois and Williams[5] substantiated some previous experimental work by Lamson et al[6] to the effect that glucose prolongs the narcosis produced by Pentothal sodium in dogs. They found that adenosine triphosphate and adenosine-5-monophosphate will immediately awaken dogs from certain stages of narcosis.

Although 3 patients roused from uremic coma by $A_8MP$ is not a sufficient number to justify considering this drug a specific form of therapy, we feel that the drug definitely merits further investigation. Its use is theoretically logical in uremic coma and perhaps in other types of metabolic coma.


## SUMMARY

Three patients with uremic coma were roused from coma with adenosine-5-monophosphate. Further investigation along this line is indicated.


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# Contributions to the Study of Nerve and Muscle Interrelationship

## Studies in the Pathologic Physiology of Poliomyelitis

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The treatment of poliomyelitis and degenerative nerve lesions requires a more dynamic concept of nerve function and regeneration than has hitherto been applied. This is possible by correlating the biochemical interrelationships between nerve and muscle, and the double dependence of the enzyme systems and substrates of both nerve and muscle on the adenylic nucleotides.

It is striking that in the simplest viruses, consisting of only one type of protein, such as the simple plant viruses and the poliomyelitis virus, ribonucleic acids are present. It appears that all viruses interact with the host cell as parasites on the system for protein production. Analysis could show that different viruses intrude in different phases in this system. Casperson[1] studied the virus elements in the cells at the time of their growth. In the more complicated viruses it was evident that during reproduction a ribodesose nucleotide mechanism operates, namely, the general nucleic acid mechanism for protein synthesis and the specialization thereof for the reproduction of several proteins linked together in the chromosome mechanism. The simplest viruses consisting, as far as we know, of only one type of protein also contain nucleic acid but of the ribose type.

Observations on the nucleic acid metabolism in the infected cell show that all viruses studied appear as parasites on the system for protein formation of the host cell, indicating that their own systems for that purpose are incomplete. The larger viruses contain ribodesose nucleotides during reproduction. Casperson offers a simple explanation for this. The chromosome mechanism is nature's way of distributing genes of a number of different kinds evenly among the daughter individuals. The essential thing is that the different groups are linked in long chains, the gene string.

The nucleic acid mechanism operates in different types of protein synthesis, but in the gene string there is a special kind of polynucleotide, the ribodesose type. The higher viruses are more complicated than the simpler ones and must be assumed to contain several different proteins or genes. It is to be expected that an arrangement exists ensuring their proper distribution in the daughter individuals, that is, the chain in a simple chromosome. Corresponding to that we find the specific chromosome nucleic acid, ribodesose acid, in the higher viruses. In the simplest virus, consisting of one single protein, there is no need for such a mechanism, and thus the simplest general mechanism, the ribose nucleotide mechanism, is effective.

Nucleic acid is composed of four nucleotides that are acids, each made of phosphoric acid, the pentose sugar ribose or desoxyribose, and a purine or pyrimidine base. The purine nucleotides are adenylic acid and guanylic acid; the pyrimidine nucleotides are uridylic acid and cytidilic acid in plants, or thymilic acid in animal

tissue. However, to make nucleic acid, all four of the nucleotides must be available. When a virus, such as that of poliomyelitis, becomes a parasite in the host tissues, nucleic acid must serve as its medium at the expense of all the nucleotides. In view of the active nucleotide metabolism of nerve tissue and the high requirements of nerve cells, nerve tissue is most vulnerable to the deprivation of nucleotides, and nerve function can fall below normal activity and fail to conduct normal nerve impulses.

Ramon y Cajal[2] many years ago described an experiment in which it was observed that if a nerve were exposed to vapors of ammonia gas, the conducting action was suspended while the myelin remained sound, and that degeneration of the nerve is not necessarily associated with suspension of functional activity. With this in mind, it is important to realize that the earliest restoration of nucleotide activity could bring with it restoration of nerve function. In the case of muscle function, the adenylic nucleotide system of adenosine monophosphate, diphosphate, and triphosphate supplies the muscle energy needed for relaxation; a muscle deprived of adenosine triphosphate will stay in the contracted state approaching rigor indefinitely. It follows that loss of adenylic nucleotide to the poliomyelitis virus is accompanied by loss of muscle function with resulting spasm.

Since all the nucleotides are needed to form nucleic acid for virus multiplication, the administration of the adenylic nucleotide alone could protect the muscle from energy exhaustion and counteract spasm without increasing virus reproduction. Also, with the control of the virus invasion by immune bodies, the restoration of muscle function is possible with the stimulation of adenylic nucleotide formation. It is also of vital importance that nerve regeneration be started as promptly as possible, since Howe and Bodian[3] have shown that regenerating nerve cells exhibit an increased resistance to the destructive action of poliomyelitis virus. This increased resistance occurs most strikingly during the recovery period.

It is at this stage that nucleotide therapy is urgently indicated. It is significant that the most important finding in the study of nucleic acid in nerve cell regeneration was an average decrease of phosphocreatine of about 40 per cent in regenerating anterior gray fibers, as compared with normal gray fibers on the opposite side. Since phosphocreatine regeneration is a function of the adenylic nucleotide, it is to be expected that the loss of adenylic nucleotide would be most damaging to nerve tissue and conversely that regeneration of nerve tissue would proceed more rapidly with higher levels of adenylic nucleotide and thus of phosphocreatine.

A proper understanding of nerve regeneration entails a more dynamic conception of nerve structure. Instead of being viewed as a rigid system laid down in the final form during embryonic development, nerve tissue may be said to be too active to take time for division. It is continually replacing nucleoprotein losses in axon functions. Regeneration is thus possible at various levels of functional loss. In our clinical records, regeneration after four years of conduction loss and muscle atrophy occurred. An understanding of the biochemical properties of nucleic acid and the nucleotides opens the field of nerve regeneration. A more optimistic conception of nerve regeneration should be taken.

The role of nucleic acid in mineral metabolism, particularly that of iron, was described earlier. Ramon y Cajal quotes the publication of Marinesco in 1919 stating

that iron is found in chromatin and as development proceeds the iron nucleic acid becomes concentrated in the Nissl bodies. It is also abundant in neurones of persons who have undergone amputation. It is absent, however, in old fibers. Marinesco attributes a catalytic function to iron in nerve regeneration. Therapeutically the iron salt of the adenylic nucleotide appears to be more active than the sodium.

Ramon y Cajal points out that the presence of a functioning muscle speeds nerve regeneration after nerve section. This can be further extended to include the connective tissue and skin, since impairment of elasticity of the sheaths surrounding the muscles likewise leads to muscle atrophy. The role of the sympathetic nervous system in its relationship to vascular supply for the muscle and its enveloping structures is just as important as voluntary innervation. From the extensiveness of this involvement in poliomyelitis, one may conclude that the sympathetic nervous system is one of the primary points of attack of the virus.

Invasion by the virus of poliomyelitis simultaneously robs the nerve cell of nucleotides necessary for nerve function, thus depriving the muscle of its nerve supply and depleting the muscle of the nucleotide upon which it depends for muscle energy. In effect we are dealing with a denervated muscle deprived of both voluntary and sympathetic innervation. In 1939 Cannon formulated the law that denervated structures become supersensitive to chemical agents. This laid the groundwork for the studies continued by Cannon and Rosenblueth,[4] which do much to explain the supersensitivity and spasm of muscles involved in poliomyelitis. They showed that denervation lowers the threshold to acetylcholine and elicits two types of responses from the striated muscle. One of these, a contraction, includes the initial appearance of propagated muscle impulses; the other, a contracture, is a reaction not attended by the development of spike potentials. The concentration of acetylcholine that will initiate muscle impulses in denervated skeletal muscles is less than that necessary to stimulate normal muscles. Where the loss of energy-producing adenylic nucleotides is great, we would expect flaccid paralysis, whereas loss of the nucleotides primarily by the nerve supply would produce a spastic paralysis.

In the recovery phase of poliomyelitis and degenerative nerve lesions, the capacity to induce muscle function by lowering the amount of stimulation necessary to elicit the response makes muscle function possible from a nerve unable to supply enough stimulation for muscle action. Actually the loss is quantitative rather than qualitative even in advanced cases of long standing, as judged by the records of recovery. Cajal had already shown that when an end organ is made to function, nerve regeneration is remarkably speeded up. This is precisely what happened clinically in the reported cases, and it is the basis for the rationale of treatment.

The approach is threefold. One approach is nutritional, by restoring nucleotide function to nerve and muscle through the supply of iron salt of the adenylic nucleotide, as well as an abundance of amino acids after the acute invasion is immunologically controlled; another approach is the early use of the muscles through the relief of pain and enhancing effect of sympathetic block at the sphenopalatine ganglion, and a third approach consists of measures to promote the peripheral vascular supply. This last can be remarkably effected through the iron salt of the adenylic nucleotide (iron adenosine-3-monophosphate).

In studies of nucleotide action we found that the adenosine-3-monophosphate gave a more prolonged action and a greater degree of peripheral vascular effect than the adenosine-5-monophosphate. This is evident in the treatment of hypertension, where the adenosine-5-monophosphate produces little or no effect while the administration of adenosine-3-monophosphate is followed in 10 to 20 minutes by a drop of 10 to 20 points in the diastolic blood pressure and frequently a pronounced vasomotor flush. In poliomyelitis the adenosine-3-monophosphate was definitely better. When it is used as the iron salt, the blood vascular effects are still more effective.

In addition, we may look for a specific chemotherapeutic effect in the inhibiting action of adenosine-3-monophosphate in the utilization by the poliomyelitis virus of the host adenosine-5-monophosphate (muscle adenylic acid). It is significant that Skeggs et al[8] have found that purine ribose nucleotide inhibited desoxyribonucleic acid utilization by *Lactobacillus bifidus*. They found that the purine ribose nucleotides, adenylic acid (adenosine-3-phosphoric acid or adenosine-5-phosphoric acid) and guanylic acid, competitively inhibit utilization of desoxyribonucleic acid by the organism. It is apparent from the clinical results that some such inhibition may be taking place in the poliomyelitis virus, since the acute phase of the disease appears to be benefited. Three procedures are followed. One is the intramuscular use of the iron salt of the adenylic nucleotide, 32 mg. daily or every other day, depending on the progress of the patient. The second is the oral administration of 3 gr. of iron ascorbate three times daily. In cases in which intravenous iron is desired, the iron ascorbate intravenous preparation is used in doses of 10 to 20 mg. diluted in 10 to 20 cc. of saline or dextrose and administered slowly. Ferrous salts exercise a selective action on tissues, particularly muscle, and participate in the cytochrome and catalase formation so essential in cell respiration. Labile iron is a vital factor in muscle function. Supplying the iron as the salt of ascorbic acid simultaneously maintains a high vitamin C level that promotes still further oxidation-reduction functions in tissue respiration, particularly in oxygen transport. The third procedure is the use of a high level of amino acids of beef and yeast or lactalbumin containing, in addition to the elements of the B complex, a satisfactory level of cocarboxylase and manganese nucleinate for its activation. This further promotes nucleoprotein formation by making available an assured adequacy of amino acids. It is this combined approach that has yielded the gratifying results reported here.

In chronic poliomyelitis and late cases, this therapy is supplemented by injections of calcium ascorbate, since the calcium radical favors activation of adenosine triphosphate and leads to a more rapid turnover of energy-rich phosphate bonds from adenosine triphosphate. It is important, however, to create first a high level of available adenylic nucleotide in order to avoid further depletion of an already low nucleotide supply. Preliminary spectrographic studies presently being made of purine and adenylic blood levels in treated cases appear to indicate that upper normal levels are attained after iron adenosine-3-monophosphate therapy.

## CLINICAL RECORDS

*Case 1: Convalescent anterior polioencephalomyelitis.* A 30 year old married man was

admitted five days after onset with practically no function in either leg and very little useful function in either arm. Two weeks later he was able to sit on the edge of the bed. A month later he was started on Ironyl and within a month after that was able to walk with help. Two months after Ironyl was started, he walked more than 600 feet alone with a walker.

*Case 2: Convalescent acute bulbospinal polioencephalomyelitis.* A severely affected 30 year old man who had had polio about 17 months before, and who had been unable to increase his pulley weight, used in extension exercises of the left elbow, beyond 3 lb. for the previous 10 months, was able to increase the weight to 4 lb. three weeks after starting on Ironyl, and to 5 lb. two weeks later. He had previously never been able to sit more than about two and one-half hours, but two months after starting Ironyl, he was back at his engineering desk for three hours each day and could walk up and down a 25 degree ramp.

*Case 3: Convalescent acute spinal poliomyelitis.* A 24 year old married man was started on Ironyl, Ferro-C, and Co-Amino four months after onset, at which time he could barely sit alone on the edge of the bed, could push only 1 lb. with his right arm, and could barely move his legs. One month later, he could give himself a complete bath, move himself from bed to wheel chair and back alone, and required only five minute rest periods between fatiguing resistive exercises.

*Case 4: Convalescent acute bulbospinal polioencephalomyelitis.* A 14 year old boy, quadriplegic, still required a respirator about eight hours a day; he had developed moderate function of both hands and one elbow, but none in his lower trunk or either leg. When Ironyl was started five months after onset, he was able to stay out of the respirator entirely within three weeks after starting the regimen, and within five weeks he showed definite significant voluntary function of the entire left hip, quadricep, and anterior tibial.

*Case 5: Convalescent acute bulbospinal polioencephalomyelitis.* A 9 year old girl who was practically a quadriplegic had only fair function of both hands and one elbow at the time she started Ironyl five months after onset. Within one month, she was able to comb her hair with both hands and to feed herself with ease, with beginning active function in both legs.

*Case 6: Convalescent severe bulbospinal poliomyelitis.* A 6 year old boy, a complete quadriplegic, was started on Ironyl and Ferro-C six months after onset when he still required an iron lung four hours a day, and he had no other motor power except neck rotators, mastication, and slight function of both arms. Within three weeks he was permanently taken out of the respirator. While sitting in a wheel chair with his trunk elevated about 35 degrees he was able to flex the neck forward and raise his head about one inch off the pillow without aid. He was dismissed home.

*Case 7: Acute anterior spinal poliomyelitis.* A 15 year old boy was admitted three days after onset with a temperature of 104 F., severe pain, and almost complete paralysis of the right hip and knee. The pain abated and the temperature fell to 100 F. by the fifth hospital day, but there was no improvement in strength by the seventh day, when Ironyl, Ferro-C, and Co-Amino were started. Two days later all muscle tests were at least "good," and the next day the boy walked fairly well with too heavy shoes.

SUMMARY

1. The poliomyelitis virus is almost entirely nucleic acid, one fourth of which is adenylic nucleotide; it damages its host by utilizing the muscle adenylic acid (adenosine-5-monophosphate). Adenosine-3-monophosphate may inhibit the utilization of desoxyribose nucleic acid by the poliomyelitis virus and thus protect the host.

2. When a muscle is deprived of adenosine, mono-, di-, or triphosphate, its energy metabolism practically stops and it remains in a contracted state of rigor almost indefinitely.

3. Nerve and muscle tissue depend on adenylic nucleotides for their metabolism and protein production. When the muscle metabolism is interfered with, its nerve supply also degenerates, and vice versa.

4. When a muscle's nerve supply is interfered with, both the muscle and its nerve become more sensitive to vasoconstrictors, with resultant ischemia, pain, and eventual paralysis. Iron adenosine-3-monophosphate produces vasodilatation and relief from pain.

5. Decreased nerve function is associated with decreased combining power between the remaining nucleic acid and acetylcholine, with further paralysis as a result.

6. Ferrous ascorbate promotes tissue respiration and cytochrome and catalase formation.

7. Co-Amino with manganese nucleinate promotes nucleoprotein regeneration. Phosphorylation of the B complex to cocarboxylase and cozymase (necessary for nerve glucose metabolism) aids directly in cell respiration.

8. The use of the iron salt of adenosine-3-monophosphate, ferrous ascorbate, and Co-Amino has resulted in unexpected dramatic improvement in all 7 acute and convalescent polio patients in whom this treatment was used at the Miami Valley Hospital in Dayton, Ohio.

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# Clinical and Pathogenic Viewpoints on Nonbacterial Subacute Endocarditis

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Cases of subacute endocarditis with a constantly negative blood culture have been known since 1903, when Schottmüller discovered the microorganism (*Streptococcus viridans*) most frequently responsible for bacterial endocarditis. For a long time, the negative blood cultures were attributed to defective bacteriologic technique, which may have been true in some cases. Today there is no doubt that a distinct form of nonbacterial subacute endocarditis exists as a separate clinical entity.

The problem acquired its present importance when it was found that, although bacterial subacute endocarditis responded satisfactorily to antibiotics, the nonbacterial form did not.

## DIFFERENTIAL DIAGNOSIS

The incidence of nonbacterial endocarditis varies in different countries, but, in general, it is less frequent than the bacterial form. Its incidence is known to increase during unusual periods of undernourishment or unfavorable living conditions. In such circumstances, nonbacterial endocarditis becomes three times as frequent as the bacterial form. We observed this fact in the years following the Spanish Civil War. It was later reported by Aleksandrow in Poland; Gomori in Hungary; Heilmeyer et al, Schoen and Fritze, and Spang and Gabele in Germany; and Donzelot et al and Coumel et al in France, during the years following World War II. An extraordinary increase in the nonbacterial form had already been reported in Germany after World War I by Morawitz and Hassencamp, in 1921 and 1922. These unusual increases were found to be predominant in the men (80 per cent were men in the postwar series of 40 cases), probably corresponding to the greater exposure to the stresses of war, prison camps, and other hardships. In addition to these environmental factors, which we pointed out originally, individual predisposition plays an important role in the etiology of the disease.

The fundamental clinical feature of nonbacterial subacute endocarditis, as was stated earlier, is the persistently negative blood picture throughout the clinical course of the disease. This does not, however, exclude the possibility that a very brief, fleeting bacteriemia may have existed in the preclinical stage, too early and too briefly to be detected.

This possibility has not been substantiated so far, but, if it were, it would force us to revise the concept of true nonbacterial subacute endocarditis, as it is held now, and to differentiate between it and Libman and Friedberg's bacteria-free stage. Another difference would be that, despite the negative blood culture, the nonbacterial form is accompanied by fever, which is not the case in the stage described by Libman and Friedberg.

The clinical course of the nonbacterial form is more prolonged than that of bacterial cases that do not respond to antibiotics. While the bacterial forms resistant to antibiotics usually follow a fatal course in three to eight months, the nonbacterial forms generally run a course of one to three years, frequently interrupted by quiescent periods. These remissions may deceive us into thinking that an effective therapy has been discovered, but, unfortunately, this has never been the case.

There are also marked differences in the blood picture that merit consideration. As we have been able to show, nonbacterial endocarditis usually develops with leukopenia, whereas, in the bacterial form, there is leukocytosis with a more marked increase in the number of neutrophils. My co-workers (Gras and Foz) and I were able to show that these plasma changes are much more marked in the nonbacterial form than they usually are in bacterial endocarditis. Very high titers for serum proteins were frequently found, sometimes as much as double the normal rate. There was a patent inversion of the sedimentation-globulin quotient, while the Takata-Ara, formol, and lacto-gelification reactions were intensely positive, usually more so than in the bacterial form of the disease.

## THE PROBLEM OF PATHOGENESIS

Although we cannot, at this stage of our knowledge, arrive at any definite conclusions, we would again draw attention to the possibility that, in the nonbacterial form of endocarditis, there exists a fleeting preclinical stage of bacteriemia. In this connection, in histologic sections of heart valves from patients who died of nonbacterial endocarditis, it was seen that some amorphous masses, possibly remnants of an old bacterial lysis that had not developed any culturable bacteria by the time tests were made, were embedded deep in the valvular tissue. The appearance of these sections differed considerably from corresponding sections of heart valves in patients who died of the bacterial form of endocarditis.

It is entirely possible that some special immunologic factors determine the unusual evolution of nonbacterial endocarditis in some subjects. Following this trend of thought, Doumer and Lorriaux believe that the characteristics of the disease depend more on special conditions in the patient, and they identify the condition as one of Selye's "diseases of adaptation." Loeffler considers it to be a transitional or intermediate form between rheumatic endocarditis and bacterial subacute endocarditis, emphasizing its points of resemblance with Libman-Sacks' disease, the Felty syndrome, and the parietal endocarditis described by Loeffler himself.

A new pathogenic hypothesis is tenable if one regards nonbacterial subacute endocarditis as one of the so-called "diseases from autoantibodies." The intervention of autoantibodies in the pathogenesis of rheumatic processes has already been suggested by several authors, although no conclusive experiments have so far been made.

The antigen-antibody mechanism is, of course, well known. When a certain component of the organism becomes an antigen by itself, it stimulates the production of antibodies, which react with the antigen. This process of antigen-antibody reaction could account for most, if not all, of the symptoms observed in rheumatic

conditions. A good example is that of acquired hemolytic jaundice, where it is possible to see an autoantibody directed against the red blood cells. It is extremely difficult, if not impossible, to interfere with this process. The beneficial action of the adrenocortic hormones (cortisone and its analogues) appears to lie in their ability to delay the production of antibodies.

We might deduce from known facts that the heterogeneous group of collagen diseases are, in reality, "autoantibody diseases." They hold the following characteristics in common: an unknown etiology, serious systemic repercussions, and an impression that they are produced by a microorganism, which, however, is never discovered. Clinically, they follow a long evolution and have an indefinite duration; they also cause important changes in the blood plasma proteins. None of the diseases responds to antibiotics, only to the adrenocortic and corticotropic hormones.

Among these diseases may be listed acute disseminated lupus erythematosus, dermatomyositis, Libman-Sacks' disease (verrucous endocarditis complicated by disseminated lupus erythematosus), periarteritis nodosa, scleroderma, and, sometimes, rheumatic fever and rheumatoid arthritis. In the majority of these processes, autoantibodies have not been found with decisive regularity. However, my coworkers, Foz and Batalla, have been able to demonstrate the existence of an autoantibody directed against the globulin of the blood stream in patients with rheumatoid arthritis.

Considering that nonbacterial endocarditis presents all the characteristics common to the diseases produced by autoantibodies, it is proper to suggest that autoantibodies play a decisive role in its pathogenesis. In fact, we have oriented our future research on this subject in that direction. The favorable therapeutic results obtained with cortisone in some cases of nonbacterial subacute endocarditis appear to corroborate the pathogenic hypothesis we have outlined.

## CONCLUSIONS

We consider that nonbacterial subacute endocarditis, with a constantly negative blood culture, constitutes a definite clinical entity with certain characteristics that differentiate it from bacterial subacute endocarditis, with positive blood culture. These characteristics are: (1) The impossibility of isolating causative bacteria by blood culture. (2) Its protracted course. It may run two years or more, with irregular fever, possibly an expression of its septic character, which is of a lesser degree than in the positive form. (3) Its peculiar blood changes: leukopenia in contrast to the leukocytosis found in the positive form; a higher blood sedimentation rate, and especially the peculiar intensity of plasma reaction, with increased protein, inversion of the sedimentation-globulin quotient, and strongly positive Takata-Ara, formol, and lacto-gelification reactions. (4) No favorable therapeutic results with antibiotic treatment.

The pathogenesis of the nonbacterial form of endocarditis is not known. The remarkable similarity between the evolution of this form of the disease and of the so-called collagen diseases seems to warrant its provisional inclusion in this group.

It is suggested in this connection that, as has been shown in some collagen dis-

cases, the mechanism of antigen-antibody reaction may also operate in nonbacterial subacute endocarditis.

Present-day knowledge of this peculiar disorder of the immunologic mechanism opens new possibilities in the understanding of the pathogenesis of processes with a prolonged or indefinite course, an unfavorable prognosis, and showing all the clinical symptoms of an infectious disease without producing an identifiable causative agent.

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## New Look on Old Frauds

A review of the worthless, dangerous, or fraudulent devices foisted on a gullible public, published on the fiftieth anniversary of the Food and Drug Administration, makes for sorry reading. Since 1939, the FDA has chalked up 477 seizures and instituted 50 prosecutions or injunctions. Yet in spite of this vigilance, the ancient art of quackery manages to survive.*

A typical example of worthless devices was a dumbbell consisting of two plastic tumblers partially filled with water, sealed with paraffin, and joined by Scotch tape. The user had to hold this ridiculous article in his hands while keeping the feet firmly on the floor. The atoms in the body were then supposed to expand, while the dumbbell device gave off energy by "expanded hydrogen atoms" or "Z-rays." This device, costing $50, was supposed to correct obesity or abnormal thinness, diarrhea or constipation, reverse the aging process, rejuvenate the user, and, in short, cure "any disease known to mankind."

For believers in radioactivity, quackery offered a small pencil-shaped tube containing $0.002 worth of barium chloride granules. Sold for $300, the gadget was said to have radioactive powers when worn on the body as a cure for cancer, diabetes, leukemia, ulcers, and other serious diseases. Another device had a metallic cylinder from which two metal plates were suspended by wires; these plates were applied to the body while the cylinder itself was immersed in cold water. This absurd gadget was claimed to be an effective preventative and cure for most diseases, including appendicitis, tuberculosis, syphilis, paralysis, and heart disease. In this field of mysterious energy, perhaps the best known device was the so-called "orgone energy accumulator," a cabinet rather like a telephone booth, built of alternate layers of wood, metal, glass, and steel wool, with no electrical energy connections whatsoever. The box was supposed to accumulate the "orgone energy" from the atmosphere, wherever that might be, and then concentrate it into the body of the person sitting in the box. The Food and Drug Administration officials had an enormous amount of legal work to do to stop this particular form of trumpery.

It is astonishing to find how tenacious some quacks can be. One of the FDA's most troublesome cases was that of a "spectro-chrome" device consisting of a 1000 watt lamp and a cabinet supplied with colored glass slides fitting over an aperture through which colored light bathed the patient. For a modest fee of $90, the trusting citizen was bemused by literature compounded of Oriental mystic jargon and bathed in a light appropriate to his disease. Several thousand of these lamps were

* See GRANGER, G. A.: Quackery and the law, Internat. Rec. Med. & G. P. C. *169*:100–103 (Feb.) 1956. The article is one of a series of Food and Drug Administration Anniversary Editorials, which will be published in June in book form by Medical Encyclopedia, Inc., under the title of "The Impact of the Food and Drug Administration on Our Society."

distributed, and the first trial lasted 30 days, ending with victory for the government. The maker of the lamps (an East Indian) continued to ship them, at which point criminal prosecution was filed against him; this trial lasted 42 days, the government being obliged to present an array of physicians and relatives of victims who had used the device and died of the very disease it was supposed to cure. The jury found the maker guilty, imposing a fine and a suspended prison sentence. The decision was upheld by a Court of Appeals, which did not prevent the lamp-peddler from requesting a review by the Supreme Court, a move that was denied. The energy and expense involved in all this litigation, not to mention the patient investigating by FDA agents, must have amounted to several million "watts" of energy. The modern quack is flanked by skillful lawyers who take advantage of every loophole in the law to further their dishonest trade. Similar to the spectral lamp was another device that could be made for $10, and was sold for $400, consisting of "irradiated" water recommended for the cure of over a hundred diseases, including apoplexy, appendicitis, cancer, diabetes, and meningitis.

Weirdest of all quack devices was a machine that was claimed to be able to diagnose any ailment by measuring "emanations" from a dried blood spot on sterile paper. It is sad to note that a good many medical practitioners entered into the scheme, even though investigation eventually revealed that the machine was incapable of distinguishing between the blood of a bird and that of a man; on a spot of coal-tar dye, the machine actually diagnosed "systemic toxemia."

The Food and Drug Administration is to be highly commended for its untiring war on quackery of all kinds. It has developed many successful legal cases against quacks, even though its work is hampered by a lack of funds. Budgetary restrictions should not be allowed to endanger the health of American citizens, however foolish and misguided they may be.

## MD Publications' Technical Display at AMA Meeting

MD Publications, Inc., will be represented again this year at the 105th Annual Meeting of the American Medical Association, which will be held in Chicago from June 11 to 15. The 1956 display booth of MD Publications will feature (1) Antibiotic Medicine & Clinical Chemotherapy, the current developments in this dynamic field of medicine; (2) Stress, the revolutionary concept in medicine; and (3) Travel Medicine, a new branch of medicine dedicated to health in travel. The above illustration shows MD Publications' exhibit at last year's AMA meeting, which was held in Atlantic City.

Prominently displayed by MD Publications will be their seven journals: Antibiotics & Chemotherapy, Antibiotic Medicine & Clinical Chemotherapy, International Record of Medicine, Quarterly Review of Pediatrics, Journal of Clinical and Experimental Psychopathology & Quarterly Review of Psychiatry and Neurology, Quarterly Review of Surgery, Obstetrics and Gynecology, and MD.

Books published by MD Publications, Inc., and Medical Encyclopedia, Inc., during the past year will also be exhibited. These include: Fifth Annual Report on Stress 1955–56 by Hans Selye and Gunnar Heuser; The Impact of the Food and Drug Administration on Our Society (by 67 authors); Antibiotics Annual 1955–1956 (150 papers by 375 authors); Symposium on Medicated Feeds by 57 contributors; The MD International Symposia Monographs—(1) Health and Travel, (2) Medical Writing, (3) Psychiatry and Religion. Books in the Antibiotics Monographs Series are Erythromycin by Wallace E. Herrell; Assay Methods of Antibiotics by Donald C. Grove and William A. Randall; Tetracycline by Harry F. Dowling; Antibiotics in Nutrition by Thomas H. Jukes; Polymyxin, Neomycin, and Bacitracin by Ernest Jawetz.

# FOOD AND DRUG ADMINISTRATION ANNIVERSARY EDITORIALS

*In June of 1956, the Food and Drug Administration will have completed fifty years of service to this nation. In order to pay tribute to the outstanding achievements of the FDA,* ANTIBIOTICS & CHEMOTHERAPY, ANTIBIOTIC MEDICINE, *and the* INTERNATIONAL RECORD OF MEDICINE AND GENERAL PRACTICE CLINICS, *journals of MD Publications, Inc., are publishing a series of exclusive Editorials written by members and associates of the Food and Drug Administration on the various activities and different facets of the technical work that is carried on.*

## The Practicing Physician and the Food and Drug Administration

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Every doctor is familiar with the scene.

The surgeon says, "Number 2 catgut." The instrument nurse, who has already threaded the needle in anticipation of the request, clamps the needle into the needle holder and places the latter in the surgeon's hand. He in turn, without looking at the nurse, waits until he feels the instrument in the palm of his hand and then draws it into the area of his vision. A brief glance serves to verify that it is no. 2 catgut, and without wasting a moment he takes his first stitch.

Although this little drama is repeated every few minutes in countless operating rooms over the world, it is not to its dramatic qualities that I wish to call attention. Its special significance is the surgeon's faith that when he gives the order there will be placed in his hand not only a no. 2 suture properly threaded on a needle that is properly attached to a needle holder, but a sterile no. 2 suture on a needle and a holder that have also been properly sterilized; that no one will have touched the suture or the needle with unsterile hands, nor laid them in an unsterile place, nor even coughed upon them. How can he be so sure of these things? Because he knows that before he has entered the operating room, a team of nurses and attendants, properly trained and supervised and imbued with the knowledge that even the smallest mistake can be fatal for the patient, has taken all the necessary steps beforehand to deliver the no. 2 suture when the surgeon calls for it.

This picture of the surgeon at the operating table illustrates a larger area in which doctors in general take something for granted dozens of times every day. The doctor gives a patient a drug by injection or writes a prescription for it; in so doing he takes for granted that the patient will receive a pure preparation of the drug in exactly the quantity the doctor requested. Furthermore, the doctor takes for granted that this drug will not cause any undue proportion of toxic reactions. How can he be so sure? Because he knows that long before he ordered the drug a

team of physicians, chemists, bacteriologists, pharmacologists, and other devoted servants of the health of the public examined the claims of the manufacturers of the drug; studied the reports of numerous physician-investigators; often performed tests themselves; and established and will enforce the standards to which the manufacturers must conform. This group is called the United States Food and Drug Administration. Like the nurses in the operating room, they do their work quietly and with the minimum of bother to the doctor. In fact, so unobtrusive is their work that many doctors do not realize that they exist at all unless some unusual difficulty or some major catastrophe arises.

The work of the Food and Drug Administration touches that of the doctor at many points, however. He may be one of the first to try a new drug, when it is released provisionally for clinical trial. Then the reports that he makes on his cases will be sent to the Food and Drug Administration and will be considered along with others in the determination of the acceptability of, and the standards to be set for, the drug in connection with its release for general distribution.

Second, when the practicing physician learns that a new drug is available for sale he will know that it has passed the rigid tests for safety that have been set up by this Administration. Third, he will be able to ascertain, from the label and from the circular that accompany the drug, the chemical composition, the recommended doses, the indications, and the possible untoward reactions of the drug.

In the advertising of drugs, as in other advertising, statements are frequently made that are equivocal, misleading, or even false. Writers of advertising copy seem to be masters of the art of making an unproved assertion appear obviously true. The busy doctor sometimes feels that he is at the mercy of these people. He seldom has the time to look up the articles upon which the advertiser purports to base his claim. Even if he did, he might find areas of disagreement.* The Food and Drug Administration provides him a solution to this dilemma. The label and the circular that accompany the package must contain full and accurate directions for use that reflect the best informed professional opinion in that field.

Fourth, he can be sure that the drug he prescribes today will be identical in quality, quantity, and purity with the same drug that he prescribed a month ago or a year ago, because the Food and Drug Administration is continually checking on these matters by inspecting the plants of the manufacturers and by testing samples that are purchased from retail pharmacies.

Fifth, if he observes an unusual or suspicious reaction in a patient who has received a certain drug, he can notify the Food and Drug Administration in the sure knowledge that they will find out as quickly and as certainly as they can whether the reaction was due to improper preparation of the drug or to an impurity that has crept in or whether the drug has some hitherto unknown side reaction.

In addition to these services, the Food and Drug Administration is always on the alert to protect the doctors' patients from quacks and other irregular practitioners who use worthless or even harmful drugs or devices to part the patient from his money and his health.

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* Control of advertising is a function of the Federal Trade Commission.

In certain very vital areas the Food and Drug Administration gives even more help to the doctor and protection to his patients. Insulin and most of the antibiotics must be "certified" before they can be sold. In order for a batch of one of these drugs to be approved for marketing, it must be tested by the laboratories of the Food and Drug Administration as well as by the manufacturer. The drug must be proved to be efficacious and safe, rather than merely safe, as is the case with all the drugs for which certification is not required. The manufacturer is required to keep a record of the distribution of each lot, so that side effects may be searched for and, if necessary, certain lots can be withdrawn from the market. This added protection is given by the Food and Drug Administration at a cost of 0.07 cents added to the average daily dose.

Sixth, if his patient has taken a drug that was not prescribed by a physician, the doctor knows it is one that the great majority of persons can take safely without medical advice. If any of his patients have been deluded by quacks who dispense unauthorized drugs or who use worthless devices, the doctor can call upon the Food and Drug Administration to investigate and, if they find that such deception did take place, to prosecute the offender.

Finally, the Food and Drug Administration also protects the doctor's patients from being deceived with spoiled, filthy, or contaminated food.

This is a brief summary of the ways in which the Food and Drug Administration helps the doctor help his patient. When we consider that all these things are done by a small group of slightly more than 1000 government employees who are protecting the health of some 165 million people, the physician can only echo the famous words of Winston Churchill, "Never did so many owe so much to so few."

## A Food Manufacturer Looks at the Food and Drug Administration

WALTER F. SILBERSACK
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*New York, N. Y.*

To the American food manufacturer, 1956 will be a notable year, distinguished by two related events. First, June 30 will mark the golden anniversary of the enactment of our first Federal Food and Drugs Act. Second, by year-end our retail food buying is forecast to reach an all-time high of $71,000,000,000.

This record, one criterion of our people's better way of life, is a result of our democratic process of government by law. Basic among our Federal laws is the Federal Food, Drug, and Cosmetic Act as our national food law is known today The food manufacturer considers this Act and its predecessor to have been significantly contributory to the health and social and economic progress of the last fifty years, and to be essential to protect and advance the interests of the public, and the medical profession and food industry which serve it.

This Act regulates foods involved in interstate commerce. Adulteration and misbranding of foods are prohibited, thereby assuring safety and purity and the honest, informative representation of them. This law was an accelerating factor

in the orderly growth of our food economy during the last half century from essentially a local, individual effort to today's mass manufacturing and distribution with attendant benefits to the public. It forced the recognition, helped make available, and stimulated the use and advances of scientific principles in food manufacture. It provided the food industry with a safeguard to its integrity and reputation by relief from harmful and fraudulent competitive practices of a small minority segment of the industry.

Management in the food industry views our Federal food law, in part, as an instrument of the sciences and professions of nutrition and medicine, and consequently of value and utility to the practicing physician. Such value may be illustrated by four examples of typical application to the professional dietary management of foods.

First, the breadth of the definition of adulterated foods extends beyond the more obvious presence of poisonous or deleterious substance. For instance, valuable constituents may not be omitted or abstracted from a food. Neither may any substance be substituted wholly or partially for a food. Thus not only the safety of foods is protected, but also their integrity and composition, which help determine nutritive value.

Second, foods must be labeled honestly and informatively, which thus facilitates their economic and nutritional evaluation. Certain mandatory information must be declared on labels, including the true name of the food, its ingredients, the quantitative contents of the package in terms customarily used by the consumer, and the name and address of the manufacturer or distributor. Thus the consumer and his physician have ready access to detailed information that may be required for the control of medical problems of food involvement like allergies, dietary deficiencies, and others.

Third, certain foods may be standardized by regulations issued under the Federal food law as the need and desirability arise. A food standard creates an official specification for such food, which includes a specific name, and mandatory as well as optional ingredients in controlled amounts. Currently standards are fixed for many of our most frequently consumed foods, of which a few examples are breads, flours, macaroni products, canned fruits and vegetables, milk, cream, eggs, and oleomargarine. Most significantly, these standards provide for the nutritional enrichment of many of our major foods, which have been selected in conformance with the soundest principles of medicine and nutrition. Dietary management of the enriched foods is simplified with the knowledge that only such foods as conform to the official standard may be designated "enriched," that the quantity of the enriching ingredients are within safe and effective limits, and that their contribution to the minimum daily requirements is conveniently declared on the label.

Fourth, foods represented for special dietary uses must be labeled with particular specificity to convey full and concise dietary information as established by regulations issued from time to time. The regulation defines special dietary uses, in part, as "uses for supplying particular dietary needs which exist by reason of a physical, physiological, pathological or other condition, including but not limited to the

conditions of disease, convalescence, pregnancy, lactation, allergenic hypersensitivity to food, underweight and overweight."

Typical examples of special dietary food uses are the low sodium foods prescribed for the treatment of certain heart, liver, and kidney diseases and high blood pressure. The regulation for such foods requires the uniform declaration of the sodium content in terms of milligrams of sodium in 100 Gm. of the food, and in the average serving of the food. Thus the intake of sodium is more readily and accurately calculated and controlled.

The brief and over-simplified interpretation of our Federal food law by the foregoing four examples is illustrative of its value to the physician by assurance of the availability of safe and dependable foods for the nourishment, prophylaxis, and therapy of the well and the diseased.

Additional appreciation of the benefits of the Federal Food, Drug and Cosmetic Act in the food area of the public health and welfare is gained by some further, although incomplete indication of the breadth of its jurisdiction. This Act provides for the mandatory certification of all coal-tar colors for use in foods, the inspection of food plants and warehouses to prevent unsanitary conditions under which contamination might occur, the voluntary inspection and certification of seafoods, the regulation of imported foods, the seizure and harmless disposition of adulterated and misbranded foods to preclude their consumption by the public, and the punishment of violators.

The full realization of the value and benefits of the law depends entirely upon its continuous supplementation to keep pace with modern scientific and technologic progress and how effectively the law is administered.

As an example, in 1954 the Act was amended to establish exemptions or tolerances for pesticide residues in or on raw agricultural commodities or food in its raw or natural state. Of practical interest to the physician is the clearance by the Food and Drug Administration in November, 1955, under the 1954 amendment, of the first permissible use of an antibiotic, chlortetracycline, in the preservation of dressed, uncooked poultry. The permitted residue of this heat-labile antibiotic is destroyed by cooking. Thus, sensitization of the consumer to the antibiotic and the emergence of resistant strains of pathogenic microorganisms in the consumer is prevented. This new method of preservation reduces spoilage costs in the distribution and marketing of poultry and results in lower retail prices of benefit to the public.

Our Federal food law is administered by the Secretary of Health, Education, and Welfare through the Food and Drug Administration (FDA). The FDA consists of five administrative and eight technical divisions, which are Antibiotics, Cosmetics, Food, Medicine, Microbiology, Nutrition, Pharmaceutical Chemistry, and Pharmacology. The operating funds of the FDA are annually appropriated by Congress except for some self-liquidating income derived from industry-paid services. During the last few years, the annual appropriation has remained relatively unchanged at the rate of about .035 cents per capita. Last year a Citizens' Advisory Committee was appointed with the approval of Congress to assist in the evaluation of the performance and needs of the FDA. This Committee recognized the increasing

burden on the FDA caused by our growing population and economy, and the quickening pace of science and technology. The question of the safety, nutritive value, and acceptability of foods exposed to atomic warfare or to radiation controlled for purposes of food sterilization and preservation is but one example. This Committee recommended a three- to fourfold increase of the operating budget over a period of 5 to 10 years and a separate appropriation to construct a modern headquarters building into which may be consolidated its now inefficiently separated housing.

It is the vital concern of every citizen, particularly those in the medical and food professions and industry, to be alert to the need of additional resources to the FDA. Through it are coordinated to the public the increasing benefits of our expanding medical and food sciences so essential to the security of our nation upon which rests the welfare of the free world.

## The Food and Drug Administration Prepares a Case for Court

JOSEPH L. MAGUIRE
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*Department of Health, Education, and Welfare*
*Washington, D. C.*

An important aspect of the varied functions of the Food and Drug Administration, Department of Health, Education, and Welfare, is the enforcement of the provisions of the Federal Food, Drug, and Cosmetic Act. Enacted in 1938, it has been amended in several important respects.

The Administration recommendations for enforcement are sent to the Department of Justice, either to the Attorney General, or, upon his authority, directly to a United States attorney. The cases are of three types: seizures of interstate shipments of adulterated or misbranded food, drugs, devices, or cosmetics; prosecutions for violations of the Act; and injunctions to prevent prospective criminal violations.

The operating procedures adopted by the Administration for its several divisions are geared to mesh smoothly when it becomes known that a trial impends. Apart from the issuance of supervisory orders that initiate an investigation, the first steps taken along the route to a court contest are usually by Administration inspectors. Their educational qualifications are high. Most are college graduates who have majored in a science, such as chemistry, biology, or pharmacy. Their training and instructions, while apprenticing, are directed to the execution of the minutiae of each assignment with such a degree of attention to detail that the work product, if subjected to judicial scrutiny, would not be found wanting. Standard forms that they use for documenting the collection of samples and for notices of factory inspection and the requirements for the reports of their investigations have all been planned with the objective of possible use for or at trial.

The collected sample, meticulously documented, identified, and sealed, is transmitted and assigned to an analyst at one of the district laboratories. If highly

specialized equipment, training, experience, or knowledge is required, which is not available in the field, the sample is sent to the Washington headquarters and there assigned for special attention.

The labeling, work sheets, and reports of the analysts are reviewed by the chief of the division or supervisory officials in the several districts. If it appears that a violation of the Act has been committed, the alleged violative goods are available, and there is proof necessary to establish movement in interstate commerce, a recommendation to seize is made. All supporting data are forwarded to Washington for review, and, if the recommendation is concurred in, the matter is sent to the Food and Drug Division of the General Counsel's office. It is reviewed there before transmittal to the Department of Justice. Prior to the institution of criminal prosecution, the Act specifies the alleged violators be given an opportunity for a hearing. Disclosures at the hearing are considered in determining whether prosecution will be recommended. Except for the hearing, similar study, review, and checks are made before a case is sent to the Attorney General for injunction proceedings.

If the article in litigation is a device, an Administration physicist will enlist the aid of a professor in the chemistry, physics, or electronics department of a university to make tests or studies in addition to those made in the Administration laboratory. The prestige of such scholastic attainments, his nonpartisan academic interest in the problems entailed, and the reputation of the institution with which the professor is affiliated lend prestige to the Government presentation. A court and jury can scarcely fail to be impressed when a Geiger counter, used in a courtroom test by the professor, remains ominously undisturbed by a gadget claimed to cure the gamut of human ills from warts, hiccoughs, and dandruff to diabetes and cancer by means of radioactive emanations.

In a drug or device case where unwarranted claims for therapeutic effects are made, a physician member of the division of medicine may solicit the assistance of an outstanding clinic or university hospital in order to take advantage of the advanced procedures, thinking, and knowledge that prevail there. Such aid is invariably granted. Testimony of clinical studies proving the worthlessness of the claims for the medicament are disclosed in court.

The help of individual physicians who are highly qualified in their respective specialties and who usually practice in the locale of the court's jurisdiction is frequently sought and readily granted. These practitioners, where the prevailing circumstances are appropriate, will conduct examinations and tests using authenticated material furnished by the Administration. Their expert opinions based on the results they have observed and the facts they have found are presented in support of the Government's charges.

Associations of product processors, distributors, and affiliated organizations extend their cooperation by furnishing information and, on occasion, testimony to support the Government charges of adulteration or misbranding perpetrated by an unscrupulous operator.

In cases where a product, after shipment in interstate commerce, has become violative, by reason of the misdeed of another, shippers willingly furnish the testi-

mony to show the article was legitimate when shipped. Many of these instances have occurred in the last few years in trials involving the improper sale, at retail level, of prescription drugs.

The case as it is presented at trial reflects the coordination of the various divisions of the Food and Drug Administration with able assists from cooperating clinics, institutions, physicians, other professional personnel, associations, legitimate industry, and many others solicitous of protecting the public.

Administration appropriations, it is well known, are low. Personnel is thereby sharply limited and investigational surveillance curtailed. It is an encomium for the vast majority of persons and firms engaged in supplying the American public with the vital and essential items covered by the Act, estimated at approximately $65 billion per annum, that but a minute number of the shipments made are of violative products for which enforcement actions are instituted. It is a tribute, too, to the scrutiny and good judgment of the Administration that but few cases it submits for litigation are contested. Of the latter, a minimal number have terminated unsuccessfully over the years.

## A Representative of American Labor Looks at the Food and Drug Administration

LEE W. MINTON
*International President, Glass Bottle Blowers' Association of the United States and Canada*
*Philadelphia, Pa.*

*While Congress drags its feet, we are getting horse-and-buggy protection for our health and pocketbooks. What is needed is more "muscle" for the FDA!*

The health of the people depends upon at least the full implementation of all existing health programs, each of which is an integral part of the whole problem. As trade unionists, we are not only concerned with in-plant health but with community health as well, i.e., the health of the worker's family and those around him in his community. Moreover, we are not only interested in adequate medical facilities and an adequate national health program for clinical treatment of disease and illness, but with an adequate program for preventing disease and illness.

Like the spokes of a wheel, each program must be a strong and functional part if the whole program is to run smoothly and effectively. Unfortunately, one of the few spokes of the nation's wheel of health is badly in need of repair. I speak of the Food and Drug Administration.

Fifty years ago, Congress recognized that the American public was experiencing tragic consequences from being exposed to disease and insanitary foods; addiction or toxication from harmful drugs; fraud from mislabeled or adulterated foods, drugs, and cosmetics. To safeguard the American consumer from these effects, the Food and Drugs Act of 1906 was passed and the Food and Drug Administration (FDA) was created to establish standards and regulation of these industries.

Fifty years ago the situation was serious and was recognized as such. Today it is even more serious, but reactionary and selfish motivations of a few are hood-

winking Congress into virtually repealing its original legislative intent by inadequate appropriations to enforce the law.

Every home in this nation uses foods, drugs, and cosmetics over which FDA has jurisdiction. The value of products sold and distributed subject to FDA regulation is estimated at more than 60 billion annually with more than 100,000 establishments involved in manufacturing, processing, or distribution that are subject to inspection. Despite a population increase of more than 85,000,000 persons since 1906; despite a tenfold or more increase in the number of manufacturers, processors, shippers, and retailers; despite an almost fantastic change in the quality, quantity, and types of foods, drugs, and cosmetics through research and development, Congress, year in and year out, appropriates funds to an extent that would not even be sufficient to administer the Act adequately in the horse-and-buggy days of 1906.

The Federal Food, Drug, and Cosmetic Act of 1938 requires foods to be pure, wholesome, and free of any filth or decomposition to which disease can be traced. It requires drugs to be safe yet fully potent and properly labeled to direct proper use. It requires that cosmetics be safe for human use. It requires that all three meet established standards of quality and quantity when sold to the public.

Without even thinking of expanding over-all areas of responsibility and programs, an action that in itself is much needed and justified, FDA cannot even keep up with its previously established projects. Regular and periodic inspections by field personnel for enforcement purposes are ridiculously inadequate owing to lack of appropriations to hire necessary field personnel. Approximately 200 field inspectors are trying to cover 100,000 establishments, which has resulted in only 10 per cent of inspection coverage. At this rate, each establishment covered by the Act can expect an inspector once every 10 years. Of course, FDA has tried with its limited personnel to schedule inspections based upon relative urgency and need. Accordingly, some areas of coverage receive more inspections than others, but the fact remains that the law calls for full enforcement and hence full and complete inspections of all covered establishments. Of approximately 17,000 grain and flour establishments subject to inspection, the average yearly number inspected has been approximately 500. This in face of known and constantly recurring instances of sale and processing of diseased grain. As another illustration, the Amalgamated Meat Cutters and Butcher Workmen of North America-AFL have for years complained to government and industry that sick and diseased poultry is being processed and sold to the American housewife.

It is now common knowledge, except to the public in general, that filth and disease exists in certain parts of the poultry industry. Most shocking of all revelations is the high rate of diseased poultry that certain segments of this industry place on the dinner tables of American homes. All this is taking place despite the fact that science has proved that there is direct similarity of disease between poultry and man, and that man is more susceptible to contacting disease from poultry than from any other food source.

When a poultry operator is caught preying upon the public and jeopardizing the nation's health by selling diseased poultry, he quickly pleads guilty, or nolo-con-

tendere (a legal defense of accepting criminal conviction), and pays a nominal statutory fine. He then hurries back to his filthy and insanitary plant to spread more disease knowing that an FDA inspector will not reach him again, on his long list of establishments to inspect, for months to come, if ever.

These are but two examples of how thousands of food processors are deliberately jeopardizing the health of this nation. Similar situations exist in the drug and cosmetic industry. Traffic in adulterated drugs, even more lethal in their effect upon human lives, is becoming more widespread due to consumer ignorance of labels or preparations. The same holds true for cosmetics. Naturally, reputable food, drug, and cosmetic concerns are not involved. They never think of illegal marketing nor have any reason to subordinate public interest to their own profit status. Rather it is the "fly-by-night" manufacturer or processor who, in cahoots with the disreputable butcher or pharmacist, prey on the public. There are so many of these little and scattered operators that the job of proper investigation becomes more difficult and requires more manpower to cover such a vastly scattered area than ordinarily realized.

Apart from the very important health aspects of this over-all problem of inadequate FDA inspections, there are also economic aspects involved. As trade unionists representing the largest individual group of consumers, we must insist that the Act be fully implemented to prevent fraud upon the consuming public. Not only have the health responsibilities of FDA lagged far behind but the "economic responsibilities" have of necessity only received passing attention. By "economic responsibilities" the law was intended to protect the consuming public from being swindled by disreputable food, drug, and cosmetic manufacturers or processors who fail to maintain minimum quality and quantity standards. It is impossible to determine accurately the hundreds of millions of dollars lost each year by the consumer as a result of deliberate cheating in the quality and quantity of foods, drugs, and cosmetics. In adulterated drugs alone, the estimate runs from $50,000,000 to $120,000,000 in yearly traffic.

Also in the area of economic responsibility a serious problem is recurring that results indirectly from that of inadequate FDA investigation activities and that relates to the working conditions under which insanitary foods and adulterated drugs are manufactured or processed. Although FDA does not have jurisdiction over working conditions in these industries, it does attempt to establish programs for plant cleanliness as such would relate to purity of foods, drugs, and cosmetics. Working among filth and disease is no less damaging to the healthfulness of human beings than it is to the healthfulness of foods. The same selfish profit motivations that go so far in jeopardizing the health of this nation are also undermining the health of employees working in these "fly-by-night" installations. Proof of this relationship is evidenced by a recent case of a diseased food product found to be manufactured in a "home industry." "Home industries" date to the sweatshop era when workers were forced to toil in cellars and lofts for long hours under horrible conditions. Since not all of these leeches are able to operate openly and in flagrant violation of the law, many locate themselves in cellars, lofts, and garages

and operate not only in violation of the Federal Food, Drug and Cosmetic Act but in violation of other federal, state, and municipal health and safety laws.

Fortunately, to correct the problem, no lengthy and time consuming task of enacting legislation is involved. The necessary legislation and enabling authority exist. All that is required is for Congress to appropriate sufficient funds for inspection purposes, so that the Food and Drug Administration can properly discharge its responsibilities in protecting the public, its health and pocketbook.

## A Practicing Attorney Looks at the 1938 Federal Food, Drug, and Cosmetic Act and Its Administration

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A lawyer should first approach this Act from the viewpoint that it is a great public law of profound social and economic importance to our country. The Act governs our most essential food and drug industries and regulates our most essential food and drug products, and it does so for the essential purpose of protecting the public health by prohibiting an injurious adulteration or misbranding of its products.

Hence it is a basic public health law. But it is more than that, for it is also a basic agricultural law by reason of its application to agricultural foods. For example, it establishes standards for their purity and controls their pesticide contamination. It is further a basic nutrition law to improve the national diet. Thus, among other things, it establishes standards for needed enriched foods, and it safeguards dietary foods. In addition, it is a basic pharmacy and medical law, to assure the safety, purity, and efficacy of necessary drugs and medicines.

A lawyer should next approach this Act from the viewpoint that it likewise has a profound legal importance, in itself, for two historic reasons. The first reason is that the predecessor of this Act, the original 1906 Federal Food and Drugs Act, was the third major law enacted by Congress to regulate interstate commerce at all. The other two laws were the 1887 Interstate Commerce Commission Act, to prevent discriminatory charges by railroads, and the 1890 Sherman Antitrust Act, to suppress wrongful private monopoly. The second reason is that the present 1938 Act uses a regulation of interstate commerce to regulate intrastate commerce as well. For it jurisdictionally reaches all intrastate commerce in its products, where they originated in interstate commerce; and all intrastate commerce in oleomargarine, even if it never entered interstate commerce, which is a significant extension of the Federal Government to control local affairs also.

For these reasons, the legal profession must give the Act before us a high place in our socioeconomic history and in our national jurisprudence, a statement emphasized by the following practical fact: The law of this Act and its predecessor has been the legal basis for the incredible renaissance of our food and drug indus-

* The Institute was established by leading food manufacturers to provide a better knowledge of the food and drug law by university instruction and basic research.

tries in the first half of the twentieth century. It has freed them from the restraint of destructive product competition; it has thus released their creative genius for beneficial exercise in our dynamic free enterprise system; and it has thus permitted them to make constructive use of their infinite scientific and technologic resources. As a result they have made greater progress in food and drug improvement in the last 50 years than ever before, and they have provided our people with the highest food and drug standards yet achieved. Hence it is most fitting that we commemorate the fiftieth anniversary of this public law in 1956, which is the one of greatest importance to the largest number of our people, to wit, the consuming public.

Moreover the legal profession should also recognize that this Act has been superbly administered by the Food and Drug Administration, as a rule. This I know from my own professional experience with its administration, for more than 40 years. The FDA is an expert and career professional agency of the Federal Government, specially organized to administer this Act; it is directed by able executives and competent scientists; and it is manned by dedicated public servants. The FDA has the tremendous responsibility of protecting every man, woman, and child in this country from death or injury by the adulteration or misbranding of food and drugs, and it has successfully met this responsibility, notwithstanding the handicap of inadequate appropriations. But fortunately that situation is in process of repair through the corrective report last year by the Citizens Advisory Committee, which is now beginning to receive due implementation by Congress.

## Leaders of the Food and Drug Administration

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The papers gathered under this cover were written by members of the Food and Drug Administration and a few close observers in commemoration of the Fiftieth Anniversary of the first Federal Food and Drugs law. The original Food and Drugs Act was signed by President Theodore Roosevelt on June 30, 1906.

To appreciate fully the evolution from a simple beginning to the complex structure of food and drug control today, requires some knowledge of the history of its staff.

Dr. Harvey W. Wiley, who became Chief Chemist in 1883, began with two or three laboratory assistants and a secretary working in a single basement room in the original Department of Agriculture building. Soon the group moved to a separate building—after a laboratory explosion that perturbed the Commissioner of Agriculture (it was not until 1889 that the Department of Agriculture had a Secretary). When the Division was organized as the Bureau of Chemistry in 1901, it numbered less than 40 people.

Dr. Wiley's struggle for the enactment of the first Federal Pure Food and Drugs law lasted 23 years—first in the laboratory where the analytic data were developed and understood only by trained scientists. Then, in the last few years before the

law was passed, the struggle took on the aspects of a popular crusade in which its leader earned the title "Father of the Pure Food Law."

Dr. Wiley began administration of the new law with no background of enforcement techniques, no judicial guidance, and only a small staff of trained chemists responsible for all phases of agricultural chemistry. A fair amount of information had been built up concerning prevailing adulterations and misbrandings.

The entire next year was devoted to setting his house in order to work with the new law, a preoccupation also shared by the industries that would come under its control.

Regulations were drafted, civil service examinations held to secure inspectors, and the analytic force augmented. The original group of inspectors numbered 28. As soon as he looked over the new recruits, Dr. Wiley named Walter G. Campbell Chief Inspector—a step that had a profound influence on the course of food and drug control. Mr. Campbell, an attorney by profession, was to prepare the first seizure libel and direct the enforcement work for a longer period than any man in its history.

Dr. Wiley's enforcement years were turbulent up to the time of his resignation in 1912. Not only was there opposition from some segments of the affected industries but also strife within the Department of Agriculture, which resulted in a curbing of many of Dr. Wiley's activities. Despite these factors, an observer of the entire period of Federal enforcement has stated: "All in all, there never was, before or since in so short a time, such an extensive revolution within the food industries as took place between 1907 and 1912. Never since have conditions in the food industries even approached those existing before the pure food law of 1906 became effective." The drug revolution was slower and came largely under the 1938 revision of the law.

After Dr. Wiley's resignation, R. E. Doolittle served as Acting Chief for nine months until Dr. Carl L. Alsberg was appointed Chief Chemist. Dr. Alsberg, a brilliant research biochemist, greatly strengthened the fundamental scientific basis of the Government's operations and also the education of producers to improve their products through scientific controls. Inexperienced in regulatory operations, he soon found that he needed a competent and trusted assistant to direct the enforcement functions. In 1916 he appointed Mr. Campbell Assistant Chief, in charge of regulatory work.

Under various titles and organizational changes, Mr. Campbell directed food and drug enforcement until he retired in 1944. He also served as director of regulatory work for the entire Department of Agriculture from 1923 until 1933. Dr. Charles A. Browne, who was Chief Chemist from 1923 until the Food and Drug Administration was organized as a separate unit in 1927, also directed the research and technologic work and left entirely to Mr. Campbell the administration of the Food and Drugs Act. Mr. Campbell was the first Chief of the Food and Drug Administration and leader of the move for a better law, which was enacted in 1938.

His successor was Dr. Paul B. Dunbar, who had also entered the Bureau in 1907, having just received his Ph.D. in chemistry. He became Mr. Campbell's staff assistant in 1914 and Assistant Chief of the Bureau in 1925. He was the first

Assistant Chief of the Federal Drug Administration, and, in 1942, he became Associate Commissioner. This team of lawyer and scientist throughout these years established the sound policies that are still guiding the Federal Drug Administration staff.

When Dr. Dunbar retired in 1951, he was succeeded by Charles W. Crawford, whose 34 years in the organization had been highlighted by liaison work with legislative advisors and members of Congress who sponsored the Federal Food, Drug, and Cosmetic Act of 1938 and by drafting regulations for its enforcement and the formulation of food standards. Appointed as a chemist in 1917, he had served as Chief of the Interstate Division, which formerly directed domestic enforcement activities, and then as Assistant Commissioner and Deputy Commissioner.

His successor in 1954 was the present Commissioner George P. Larrick, who had joined the Federal Drug Administration as an inspector in 1923. Like his predecessor, he was an active participant in the struggle for the 1938 law, with particular responsibility to inform the public of the obsolescence of the 1906 law. He became Assistant Commissioner in 1945, Associate Commissioner in 1948, and Deputy Commissioner in 1951.

This continuity in the service has extended from top administrative officers to laboratory assistants. In January, 1937, there were 47 people on the Federal Drug Administration's active rolls who had been in the old Bureau of Chemistry when the law was enacted or joined it before the end of 1907, the first year of enforcement. Included were the Chief, Assistant Chief, five Division Chiefs, nine Field Chiefs, a number of analysts, inspectors, and clerks, and the cook for the "Poison Squad." The "charter members" have now all retired, but 21 of them are very much alive today. Approximately 25 per cent of the current staff entered the service before these 47 were honored in 1937. We are now in a second generation of food and drug control with most of those now in charge of operations trained by the pioneers.

Not only the Commissioner and his associates but also all of the District Chiefs have been promoted from the ranks of inspectors and analysts. They agree with the man who said, "If we can see farther than our ancestors, it is because we are standing on their shoulders."

Some of the papers in this volume reflect the evolution of the science and art of food and drug regulation in the continuous struggle to keep pace with affected industries and changing conditions. We have come a long way from Mr. Campbell's first handwritten libel to the complicated processes required to present a court case today; from the few analytic methods Dr. Dunbar found when he reported in 1907 to the 1000 page Official Methods of Analysis of the Association of Official Agricultural Chemists published in 1955; from the drugs and their testing methods in the eighth revision of the Pharmacopoeia to those in the fifteenth revision now governing official drugs—in the fields of pharmacology and nutrition not even contemplated in 1906—and from the early reluctant and suspicious attitudes of the industry members who first resisted the law to the acceptance by many of the working principle that the interests of Government and industry are

identical. The discussions of today's complex problems in this volume, however, show clearly that Federal Drug Administration recognizes that it is only part way through its evolutionary process.

## Measurement of Vitamin Potency

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In the first decade of this century this country was at peace with the world, and most food chemists were satisfied that classified methods of analysis for nitrogen, fiber, soluble carbohydrate, and ash content of foods yielded all the information necessary to assess the nutritive value of our food supply. However, during the second and third decades, it was discovered that foods contain additional nutritive qualities and that vitamins, present in extremely small amounts in foods, are essential for life. With knowledge of their importance, methods of measuring their presence were soon developed. A new science of nutrition has grown up, based largely on the knowledge of vitamin content of foods, and the physiologic function of these factors in the growth and metabolism of man and animals. Progress in the development of this information has been dependent upon the ingenuity of the chemist in devising new and novel means of measuring the presence of complex and sometimes unstable substances found in quantities expressed, not in terms of ounces, or per cents, but as parts per million, or as micrograms, a millionth part of a gram.

For the most part, discovery of vitamins was made by observing physiologic changes in animals maintained on artificial or purified diets that were so constituted as to be devoid of one of the essential nutrients. For example, rats or chicks fed a ration heated under specific conditions were observed to develop a syndrome called polyneuritis. When it was learned that this was the result of a deficiency of thiamine, destroyed in the ration by the heat process, the deficient animal served as a means of detecting the presence of thiamine in any test substance added to the diet. Under strictly controlled conditions, such a measurement was made quantitative, with an acceptable degree of precision.

For a number of years the U.S.P. method for determining thiamine was one involving the cure of polyneuritis in rats under carefully controlled conditions. Today vitamin D is the only vitamin for which the official method involves the use of animals.

Measurement of vitamins in animals by biologic assay methods is difficult, time-consuming, and costly. Chemists were encouraged to find more rapid means of detecting these complex substances, not only in foods, but in tissues of animals to guide the search for the way the vitamins function in the animal body.

In the 1930's, when a number of the vitamins were isolated, crystallized, and synthesized, more was learned of their chemical properties, some of which could be used as a basis for measurement. For example, it was learned that fluorescence

is a property that is useful in detecting quantitatively minute quantities of riboflavin in a solution of known volume. Thiamine was found to undergo a chemical reaction upon oxidation in alkaline solution to form a new compound called thiochrome, highly fluorescent in ultraviolet light. This property of fluorescence is the basis for quantitative measurement of both thiamine and riboflavin, by chemical methods that have been adopted by chemists throughout the world. The U. S. Pharmacopoeia contains descriptions of these methods. In wide use also are chemical methods for niacin and folic acid, based upon development of color that can be measured in a suitable photometer.

Vitamins, like all other compounds, have the property of absorbing light at specific wavelengths. Vitamin A, for example, has a maximum absorption of light at a wavelength of 328 millimicrons. If a vitamin capsule or tablet containing vitamin A is saponified by treatment with alkali in alcoholic solution, then extracted in petroleum ether, and finally further purified by selective adsorption and elution on a column of alumina (chromatography), the final solution containing vitamin A may be examined in a spectrophotometer, and the vitamin A estimated from the amount of light absorption at an appropriate wavelength. This is now a commonly used accurate technique for those substances that are sufficiently pure, or that can be purified without difficulty.

Another important analytical tool used to measure vitamin potency is called analytical microbiology. This involves the use of a microorganism, a *Lactobacillus*, for example, that is induced to grow in a purified medium, to which are added small, graded amounts of the vitamin under study. We know that the bacterium *Lactobacillus arabinosus* cannot grow if its culture medium is devoid of pantothenic acid. When a small fraction of a microgram of this vitamin is added to a test tube containing the medium, the organism will grow and produce acid that can be measured by titration with alkali. Or, if the analyst wishes, the amount of growth, and therefore the amount of vitamin, is determined by measuring the increase in the turbidity of the liquid. This kind of approach has been most useful, not only for vitamin determinations, but for estimation of amino acids, as well as for identifying many of the intermediary compounds of animal metabolism.

Present-day procedures for control of the vitamin content of pharmaceutical products and enriched foods are rapid and precise. While the bioassay requires weeks for a result, most of our vitamin methods are now completed in a few hours. From careful studies of reproducibility of methods, and of the differences in results from one laboratory to another, control chemists have learned to measure vitamin potency to within a few per cent of the true value.

Pharmaceutical and food industry laboratories are well equipped to make certain that the products they produce contain within narrow limits the vitamin content indicated on the label.

In the regulatory program of the Food and Drug Administration, the methods used for the examination of the vitamin content of products in interstate commerce are those described in the U. S. Pharmacopoeia and in the AOAC Book of Methods. These procedures have been established as reliable and acceptable by collaborative study in a number of laboratories. In maintaining a sound and effective regulatory

program it is important to have analyses of this kind conducted by chemists who have been trained to use these complex methods. A high degree of precision is important in assuring the physician and the patient that the products of commerce are of labeled potency.

In the Food and Drug Administration's laboratories there is a continuing program of study to improve these methods and also to develop new ones. This has paid dividends in the saving of time by utilizing shorter procedures, and in improved precision. Such improvements continue to increase the coverage that can be given to products bearing nutritional claims that are subject to the Food, Drug, and Cosmetic Act. More rapid analyses make it possible to remove from commerce before they are distributed to the consumer those products that are seriously adulterated. There is more to be done. With the appearance of new claims for nutritional value, and for unusual benefits that appeal to the consumer, new methods of testing must be devised.

## A Cosmetic Manufacturer Looks at the Food and Drug Administration

RICHARD SALOMON
*President, Charles of the Ritz*
*New York, N. Y.*

Some cosmetic manufacturers recall vividly their original reactions to news they received in 1938 that henceforward their activities would come under the scrutiny of the Food and Drug Administration.

At that time the cosmetic field had to some extent surrendered its claim to public belief in its advertising and labeling. Many of us recall well a flood of turtle oil creams and other concoctions that promised complete miracles of rejuvenation, and contained no turtle oil and performed no miracles. Nevertheless, most manufacturers agreed that the advent of additional Government controls was most unwelcome, and they have foretold in gloomy terms our approaching doom. Many believed that we would be hamstrung by unintelligent and unsympathetic handling of cosmetic controls by the Food and Drug Administration.

Be it said to the credit of the industry as a whole, responsible manufacturers determined to do all in their power to win the confidence of the Food and Drug Administration, and at the same time the confidence of the buying public. In its turn the FDA took an intelligent approach to the industry, sympathized with the problems we faced, and in many instances suggested methods by which we could overcome our difficulties. In no case, to my knowledge, was a purely arbitrary or bureaucratic stand taken.

As a result over a period of several years, the industry and the Administration came to understand each other. The unsound business practices of some manufacturers were abandoned, and the general buying public learned more and more to trust the advertising and labeling claims of the manufacturers of toilet preparations. Far from the doom that was foretold at the time, the industry prospered and grew. To some degree, this growth is a reflection of increasing public confi-

dence in us and in our products, and very possibly a reliance on the fact that cosmetics are known to be under good supervisory control.

Another effect upon the industry was a stimulation to creative research, which has characterized to a greater or lesser degree all of the responsible companies in our field. We have made great technical advances in our products, and up to now have not suffered undue restraint from the intelligent officials we have had to deal with at the Food and Drug Administration. That science was to play an increasingly important part in our field was recognized by the industry. At the May 1936 Convention of the Toilet Goods Association, the members unanimously voted to form a Board of Standards to study and advise the industry on questions of a scientific nature, as well as labeling and advertising claims. A few years later, the Scientific Section of this Association was formed. Scientific papers presented at May and December meetings are published in the Proceedings of the Scientific Section, which is the first American technical journal devoted exclusively to the cosmetic field. A professional scientific society in our field has been formed; namely, The Society of Cosmetic Chemists. This Society has branches in England and other countries. The Journal of the Society of Cosmetic Chemists is esteemed and respected throughout the world. Scientists of the Food and Drug Administration have presented 15 papers before the Scientific Section of the Toilet Goods Association. These excellent studies made in their Washington laboratories have been of great help in guiding the progress of our industry with special reference to safety and efficacy.

All of these moves on the part of a responsible industry, whose products are vital to the consumer, have been fostered in the atmosphere engendered by Congress' decision to place the manufacturing of our products and their packaging under the auspices of the Food and Drug Administration.

In facing the future it is my belief that most manufacturers are pleased with the progress to date and with the attitude of the Administration. We believe that it would be helpful if the budget of FDA were to be increased so as to provide funds for some basic research, which most of the companies in our field are incapable of undertaking either individually or collectively. Such research on the effects of raw materials on the human body would be most helpful and greatly welcomed by an industry that is today determined to work as closely as possible with the FDA.

NEW PAVILION FOR ST. ELIZABETHS HOSPITAL. The new $6 million Dorothea Lynde Dix Pavilion opened at St. Elizabeths Hospital in Washington, D. C., provides for 420 beds, and will operate as a receiving and intensive psychiatric treatment center with therapeutic and rehabilitative facilities and personnel.

W. M. A. SECRETARIAT MOVE. On May 1, 1956 the Secretariat of the World Medical Association and the United States Committee, Inc., will move to a suite of offices in the Coliseum Tower Office Building at 10 Columbus Circle, New York 19, N. Y.

NEW TEST FOR ANTICANCER DRUGS. Drs. David M. Greenberg and E. Norberg Sassenrath of the University of California have devised an improved method for testing the activity of anticancer drugs. The bellies of mice are injected with a determined number of cancer cells, and the animals can be killed at any time, their cancer cell-filled fluid drained, and the cells counted.

DRUG FOR HYPERACTIVE CHILDREN. Somatovite, a new drug that stimulates appetite, increases weight gain, corrects growth failure, and calms children who are hyperactive and restless, is now being marketed by the Purdue Frederick Co., New York City. It provides low-level doses of reserpine to alleviate irritability and tenseness that blocks nutritional intake, with the appetite-stimulating and growth-promoting effects of vitamins $B_{12}$ and $B_1$.

HIGH EPILEPSY RATE IN PERU. The increasing susceptibility of Peruvians to epilepsy can be attributed to a basic constitutional predisposition and certain environmental factors, according to F. Sal Y Rosas (Department of Psychiatry, Faculty of Medicine, Lima, Peru) in a report made to the Society of Neuropsychiatry. Susceptibility seems to be inversely proportionate to the latitude as well as to the altitude above sea level. Epilepsy affects 2.5 per thousand population in England compared with the unofficial estimate of 10 per thousand in Peru.

DRUG RELIEVES PAIN WHILE SLEEPING. Persistin, Sherman Laboratories' brand of salicylate esters, relieves pain of arthritic and rheumatic involvements, bursitis, neuralgias, and fever and distress of upper respiratory and other infections during hours of sleep. Analgesic levels of salicylate persist in the blood for five to eight hours following a single dose.

MEDICAL RESEARCH FELLOWSHIPS. The fellowship program of the Tobacco Industry Research Committee will be enlarged for 1956, it has been announced by Timothy V. Hartnett, chairman of the Committee. Allocation for the fellowship program this year will be $35,000; each fellowship is for $500.

RADIOACTIVE GOLD IN CANCER. Intraperitoneal administration of radioactive colloidal gold ($Au^{198}$) has yielded satisfactory results in ovarian cancer, reported J. H. Muller (Radiological Department, Frauenklinik, University of Zurich) to the International Conference on the Peaceful Uses of Atomic Energy (Geneva, Switzerland). The majority of his 114 patients were first treated surgically and then received colloidal radiogold along with standard postoperative radiation therapy. Fifty-nine per cent of the 12 patients treated, who would all have succumbed within a few weeks without therapy, had effective palliation with survival beyond six months (2 lived three years).

ARGENTINA PRODUCING SALK VACCINE. Dr. Jessie Wright, special medical consultant to the National Foundation for Infantile Paralysis, returning from Argentina, said that the country, hit by the worst poliomyelitis epidemic in its history, planned to produce Salk vaccine and to start vaccinations later this year. Cases recorded total 1773, with 165 deaths. Sixty per cent of the victims were under 4 years of age.

DRUG INHIBITS CANCER IN MICE. The American Chemical Society announced the discovery of a new drug that may show promise in the treatment of cancer. Three cooperating groups of researchers combined to report on the new drug, "D.O.N."--a shortened form of its chemical name 6-diazo-5-oxo-L-norleucine. The associated workers are at the Sloan-Kettering Institute for Cancer Research, The Mellon Institute, Pittsburgh, and the Research Division of Parke, Davis & Co. The new drug belongs to the group of amino acids.

ANESTHESIA MEASURING DEVICE. The Edin Co. of Worcester, Mass., has introduced a new instrument for measuring the depth of anesthesia during surgery. Called the "anesthograph," the instrument is a compact unit embodying the combined recording functions of the electroencephalograph and the electrocardiograph.

CANCER CELLS DETECTED. Airborne Instruments Laboratory of New York City has developed an instrument that sorts normal from cancer cells by an electronic scanning and computing device. Known as the "cytoanalyzer," the device scans the microscopic image of the cells, automatically sorts them according to their characteristics, and then classifies them as normal or suspicious.

# GENERAL PRACTICE CLINICS

This section of General Practice Clinics features reports on papers delivered at current medical meetings in the United States and abroad.

## Chronic Obstructive Pulmonary Emphysema

Presented by FRANCIS C. LOWELL, M.D., WILLIAM FRANKLIN, M.D., ALAN L. MICHELSON, M.D., AND IRVING W. SCHILLER, M.D., (Boston University School of Medicine) before the Ninth Annual American Medical Association Clinical Meeting, Scientific Lectures, Boston, Mass., December 1, 1955.

A study was conducted to evaluate the use of steroids and bronchodilator drugs in the treatment of patients with chronic obstructive pulmonary emphysema. In the course of this study, attention was drawn to the frequent occurrence of peptic ulcer and cancer of the lung. Particular interest was aroused by the frequent association of heavy smoking (which may be an important etiologic agent) and chronic obstructive pulmonary emphysema. The selection of patients was most rigid. The patients were from the Massachusetts Memorial Hospitals outpatient departments and from the private practice of doctors associated with the hospital.

The criteria for selection of patients included the following. Spirograms were made so that senile emphysema could readily be excluded. The onset of dyspnea had to have begun after the age of 40 years. This was done not because chronic obstructive emphysema was believed to begin exclusively after age 40, but in an attempt to eliminate bronchial asthma.

All cases had a slowing of expiration measured after a maximal inspiratory effort, and this was only partially by bronchodilators. Using these criteria of selection, 34 patients were studied. All had dyspnea as the primary complaint. Roentgenograms of the chest showed radiolucent lung fields with low fixed diaphragms. Nine of the patients were found to have peptic ulcer, and 2 had lung cancer.

Thirteen of these patients were placed on large doses of cortisone, up to 250 mg., given in a long single course over a period of months. Five of the 13 showed some reversibility of the disease after long periods of steroid therapy. This reversibility was measured by improvement of the spirogram records. From this study the authors conclude that steroids given to selected patients can favorably affect chronic obstructive emphysema. Steroids and antibiotics can prolong the life and add to the comfort of severely ill patients.

The 34 patients, all heavy smokers, were all more than 50 years of age. There were 28 men and 6 women. Unselected patients 50 years and more who compared with the emphysematous population were chosen, and the smoking habits of the two groups were compared. In the American population, 15 per cent of men 50 to 70 years old smoke one or more packages of cigarettes per day. In the emphysema-

tous group, 70 per cent smoke this heavily. The authors feel that emphysema arises as an inflammatory bronchiolitis as the result of long exposure to tobacco. If this is true, it also aids in explaining the occurrence of emphysema in the older age group, its preponderance in men, and the occurrence of lung cancer and peptic ulcer in the group.

## Lung Function Tests: Their Value in Medical Diagnosis and Treatment

Presented by DAVID W. CUGELL, M.D., EDWARD A. GAENSLER, M.D., AND THEODORE L. BADGER, M.D. (Harvard Medical School) before the Ninth Annual American Medical Association Clinical Meeting, Scientific Lectures, Boston, Mass., December 1, 1955.

The value of pulmonary function tests was illustrated by reviewing some problem cases that were presented to the laboratory and showing how pulmonary function tests solved the problems.

In a 23 year old man with a chief complaint of dyspnea, the history, physical examination, and chest roentgenogram revealed nothing of significance. The spirogram showed an excessive number of sighs or deep breaths at the rate of approximately one per minute. This is characteristic of anxiety states. Further questioning revealed adequate reasons for referring the patient to a psychiatrist, and considerable benefit resulted.

Two patients were presented with combined heart and lung disease. Both had mitral stenosis and were candidates for mitral surgery. Because their respiratory symptoms appeared out of proportion to the clinically evident heart disease, pulmonary function tests were performed. These demonstrated that moderately advanced chronic obstructive emphysema was responsible for many of the respiratory symptoms previously attributed to mitral stenosis.

Bronchospirometry, or the determination of the function of each lung separately, was of great value. One patient had a 20 year history of regurgitation of food and numerous episodes of pneumonia. There was some increase in the linear markings throughout both lung fields. Barium swallow revealed a gigantic, redundant, sigmoid esophagus as the result of long-standing cardiospasm. Reparative esophageal surgery was not considered possible because of the severe reduction of over-all functional capacity. Bronchospirometry demonstrated that the left lung contributed very little to the total functional capacity. A left thoracotomy was recommended, despite the already compromised total functional capacity, because of the minimal functional contribution of the left lung. A successful repair of the esophagus was performed. In another patient with rheumatic heart disease, mitral stenosis, congestive heart failure, calcific pericarditis, and bilateral adhesive pleuritis, the outcome was less fortunate. Because of the desperate nature of this patient's status, surgical relief of the calcific pericarditis was considered. As in the previous patient, total functional capacity was markedly impaired and the majority of what remained came from one side. Unfortunately, this was not appreciated by the surgeon. The "good" side was opened, and the patient expired.

The last patient presented was a 34 year old steel mill employee with considerable dyspnea on exertion that had developed over a two year period. There were minimal changes in the chest roentgenogram. Conventional pulmonary function tests were completely normal, but arterial blood gas composition and lung diffusion studies revealed marked abnormalities. Thus, there was adequate explanation for the severe dyspnea after the appropriate tests were performed. In this patient a lung biopsy revealed a marked degree of nonspecific pulmonary fibrosis.

## The Importance of Mitral Stenosis in Patients with Symptoms of Chronic Pulmonary Disease

Presented by GORDON S. MYERS, M.D., EDWARD F. BLAND, M.D., ALLAN L. FREIDLICH, M.D., AND J. GORDON SCANNELL, M.D., (Massachusetts General Hospital) before the Ninth Annual American Medical Association Clinical Meeting, Scientific Lectures, Boston, Mass., December 1, 1955.

Patients who seem to have pulmonary disease may prove to have tight mitral stenosis. The problem is to determine the relative importance of valvular disease in patients with both mitral stenosis and pulmonary disease.

At the Massachusetts General Hospital, more than 200 mitral valvuloplasty operations have been performed for mitral stenosis. In the majority of these cases, clinical acumen alone would be sufficient to select the patients properly. However, pulmonary function tests and cardiac catheterization are of great help in the problem cases. With cardiac catheterization, the catheter enters the right side of the heart and under fluoroscopy is extended into the pulmonary artery. The pressure reported at the tip of the catheter, advanced as far as possible into the pulmonary artery, approximates the pressure of the left auricle and pulmonary vein. This is called the pulmonary wedge pressure. It is normally 5 to 10 mm. of mercury. When mitral stenosis is present, this pressure is elevated by the back pressure from the tight mitral valve. When the back pressure becomes high enough, pulmonary symptoms are produced. Patients with very tight mitral stenosis may show little or no diastolic murmur.

Because mitral stenosis can give rise to pulmonary symptoms, the authors studied 12 patients whose condition was diagnosed as primary pulmonary disease but who gave some indication that mitral stenosis could be present. The majority of these patients were being treated unsuccessfully for the pulmonary disease. Among the patients were those who had been diagnosed as having bronchial asthma, bronchiectasis, pulmonary fibrosis, and unresolved pneumonia. These patients had pulmonary wedge pressures greater than 10 and up to 30 mm. of mercury. These patients were treated with mitral valvulotomy. Of the 12 patients studied, 2 were found to have low pulmonary wedge pressures, indicating that the pulmonary symptoms were not primarily due to mitral stenosis; operation was not advised in these cases.

The possibility of mitral stenosis should not be excluded in patients who present pulmonary symptoms primarily. Cardiac catheterization studies and pulmonary wedge pressures may aid in correct diagnosis. In this study of patients who had been

originally diagnosed as having pulmonary disease, catheterization revealed more patients who were eligible for valvulotomy than who were turned down.

### The Effects of Cystine and Selenium Cystine on Glutathione Reductase of Leukemic Leukocytes

Presented by JACK PENSKY, PH.D., AND AUSTIN W. WEISBERGER, M.D., (Lakeside Hospital) before the Cleveland Academy of Medicine, Experimental Medicine Section and Society for Experimental Biology and Medicine, Cleveland Section, Cleveland, Ohio, November 21, 1955.

Glutathione, which is glutamyl (cysteinyl) glycine, is an important compound in cell growth. It possesses a free mercapto (SH) group that can be readily oxidized to the disulfide (S-S) glutathione form. Glutathione reductase catalyzes this reaction, and its quantity limits the rate of the reaction.

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|---|---|---|---|---|---|---|
| GSSG | + TPNH | glutathione | 2 GSH | + $TPN^+$ | + $H^+$ |
| oxidized | reduced | ⟶ | glutathione | triphospho- | |
| glutathione | triphospho- | ⟵ | (reduced) | pyridine | |
| (disulfide form) | pyridone | reductase | | nucleotide | |
| | nucleotide | | | | |

The glutathione and sulfhydryl content of leukocytes is increased in human leukemia, and glutathione reductase may be important in determining leukocyte glutathione content.

An accelerating effect on this reaction has been displayed by versene and cystine, which act as chelating agents here. Cystine also has this effect on other dehydrogenase systems. When zinc ion is added to a solution of glutathione reductase, the zinc inhibition of the enzyme is overcome by cystine because of the latter's metal-binding capacity. In the case of lactic dehydrogenase in leukemic leukocytes, versene has no accelerating effects, but cystine does. There is thus no definite answer as to the mechanism of cystine activation of glutathione reductase. The authors believe that it may be due to the removal of metals or other impurities from the solution.

### The Differential Diagnosis of Jaundice in the Neonatal Period

Presented by ROBERT D. MERCER, M.D., (Department of Pediatrics, Cleveland Clinic) before the Postgraduate Symposium on the First Year of Life, St. Luke's Hospital, Cleveland, Ohio, October 21 and 22, 1955.

This differential diagnosis, for practical consideration, involves four entities: (1) sepsis, (2) hemolysis, (3) physiologic factors, and (4) hepatitis. In sepsis an etiologic factor should be sought in blood cultures. It may often be due to premature rupture of the maternal membranes prior to delivery. The infant should then be treated prophylactically with penicillin and streptomycin after blood cultures are taken, without waiting for the culture report. Sepsis is a more frequent cause of jaundice the more the baby is premature. If the baby appears quite ill, is not sucking, and

no definite cause is found, prophylactic treatment for possible sepsis should be started after blood cultures are taken. Hemolysis is primarily due to erythroblastosis, involving the Rh factor, and incompatibility of blood types. Erythroblastosis occurs in only 5 per cent of Rh-negative mothers, after a prior pregnancy or incompatible blood transfusion, and its severity increases with a greater number of pregnancies. It may be treated in quite mild cases by small blood transfusions, but the more severe cases, especially those with a bilirubin greater than 20, require replacement transfusions. Physiologic factors may include immaturity of the liver and increased red blood cell breakdown. Their incidence increases with the greater immaturity of the baby. Hepatitis must be considered if jaundice is not due to any of the above three factors. There is no specific method of diagnosis in the infant. It is considered infectious hepatitis and believed to be transmitted in utero from the mother. One must differentiate it from obstructive causes of jaundice which may require surgical correction. It is advisable not to operate on these babies when this differential is uncertain, as operation is tolerated poorly by babies with infectious hepatitis and the various causes of obstruction have a slow progressive course and are not generally amenable to surgical correction. Other causes of jaundice in the baby are: atresia of the biliary duct system, liver neoplasm, mucoviscidosis, annular pancreas, syphilis, pyloric stenosis at times, and the rare diseases such as inclusion body diseases, galactosuria, and toxoplasmosis.

## Current Concepts of the Action of Insulin

Presented by C. F. CORI, M.D., (Washington University School of Medicine) before The New York Diabetes Association, New York, N. Y., October 27, 1955.

At present there is considerable agreement about the nature of the metabolic disturbance present in diabetes and its counterpart, the action of insulin. The importance of intermediate metabolism, e.g., glycogen formation and oxidation, is stressed. All such transformations are initiated by the phosphorylation of glucose by adenosine triphosphate. A necessary step for all these, a common portal of entry for glucose metabolism, which is the key to carbohydrate metabolism, is the hexokinase reaction. This is thought possibly to be the chief site of carbohydrate metabolic disturbance as well as the site of the action of insulin. Underutilization of glucose in muscle is one of the basic disturbances in diabetes. Insulin increases its utilization.

Insulin acts at the hexokinase level of cellular organization, but we do not know where hexokinase is located in the different cells. There is disagreement as to whether insulin influences cell membrane permeability to sugars or acts first in the actual utilization of sugar. Either the cell regulates the rate of glucose metabolism at the membrane or this is controlled by the action of intracellular enzymes. This cannot be demonstrated in vitro, for to determine the nature of the reaction(s), the cell must remain intact.

An experiment performed to find an answer to this problem is the measurement of permeability as a rate-limiting factor in rats. A stumbling block in this experiment

is that the determination of glucose concentration in tissues cannot tell us whether the degree of hexokinase saturation has changed, since the effective concentrations are too low to be measured with accuracy. We have, however, been able to determine that heart and diaphragm muscle are much more permeable than resting skeletal muscle. Analysis of the whole bodies of rats two hours following injection of 100 mg. of sugar per 100 Gm. of rat shows that sugar disappears in proportion to the injection of insulin and in proportion to the amount of stimulation of the hind legs of the animal.

Studies show that insulin has an effect on penetration that is not specific for any particular configuration of pentose molecules; that is, it is not dependent on any particular stereochemical configuration of the pentose molecule. Glucose and pentose may penetrate into muscle by different mechanisms. Injection of glucose does not appear to influence the rate of penetration of the pentoses. In other cells, e.g., ascites tumor cells, glucose and a pentose, when given simultaneously, are found to exert mutual inhibition of penetration. The mechanism of penetration of glucose itself into muscle has not been established.

In summary, there are two possible mechanisms that could account for the regulation of glucose utilization in muscle: either the activity of the intracellular enzyme hexokinase or a specific transport mechanism that operates at the cell membrane may be assumed to be influenced by insulin. As yet there is no decisive answer.

## Empyema Thoracis in the Antibiotic Era

Presented by JOSEPH P. LYNCH, M.D., AND GERARD DESFORGES, M.D., (Tufts Medical School) before the Ninth Annual American Medical Association Clinical Meeting, Scientific Lectures, Boston, Mass., December 1, 1955.

Empyema has diminished remarkably since the advent of antibiotics. In the past two years there has appeared to be a slight increase in the disease. This is a study of 273 consecutive patients seen at the Boston City Hospital since 1940 and a group of 76 patients seen in private practice since 1946. Prior to the advent of antibiotics, approximately 120 patients a year would have been seen with empyema at the Boston City Hospital.

At the Boston City Hospital, a bacteriologic diagnosis was made in almost 100 per cent of the cases and treated accordingly. In a series of 45 of the private patients, a bacteriologic diagnosis was made in only 50 per cent. This may have been because most of the patients had been given antibiotics before cultures were taken. The authors point out that although cultures may fail to grow organisms, a gram stain of the pus may be very helpful in determining the presence of pyogenic bacteria. In the private group, 10 received medical treatment only, 2 had a closed thoracotomy, and 33 had rib resection. This does not mean that most people will need rib resection for the treatment of empyema, but only that in this small group of private patients, it would have been necessary often because too much faith had been placed in antibiotic therapy alone and the surgical principles of therapy had been neglected. These principles include drainage and sterilization of the cavity and re-expansion of

the underlying lung. This can be accomplished by thoracentesis if one is sufficiently vigorous. If there is not marked improvement in one week, further steps are indicated including streptokinase and dornase, and further rib resection if this proves inadequate.

Since the advent of the antibiotic era, the number of cases of empyema has decreased, but the morbidity of the cases has increased because too much faith has been placed in antibiotics and not enough attention has been given to the fundamentals of surgical treatment.

### Metabolism of $C^{14}$ Labeled Glucose in Diabetes

Presented by NOME BAKER, PH.D., (Radioisotope Unit, Veterans Administration Hospital, Cleveland) before The New York Diabetes Association, New York, N. Y., October 27, 1955.

The author points out that several of his co-workers have attempted to explain the many aspects of deranged metabolism in diabetes on the basis of a single enzymatic block in the ability of diabetic tissue to phosphorylate glucose ("single-block" hypothesis). He goes on to discuss evidence for and against this hypothesis based on studies from several laboratories in which the metabolism of glucose was studied both in vitro and in vivo. Apparently, it has not yet been determined conclusively whether or not the hyperglycemic diabetic without insulin utilizes glucose as rapidly as the euglycemic normal individual. The validity of a single-block hypothesis will be difficult to establish until the latter problem has been solved.

### The Use of Spinal Anesthesia

Presented by LE ROY VANDAM, M.D., (Peter Bent Brigham Hospital) before the Section on Surgery of the New York Academy of Medicine, January 17, 1956.

Spinal anesthesia is, at present, the least popular method of attaining muscular relaxation. Intravenous methods of administration are becoming the most favored, with inhalation anesthesia the second most popular.

In a situation involving muscular relaxation under conditions where abdominal surgery must be performed, the three methods of anesthesia compete with each other. When a muscle is stimulated or pulled upon, it tightens up owing to the presence of muscle tone, which is a reflex phenomenon. A muscular relaxant, such as curare, acts at the neuromuscular junction of the reflex arc. A general anesthetic, such as ether, acts both at the neuromuscular junction and at central and spinal levels as well. Relaxation with the use of spinal anesthesia is achieved by blocking nervous conduction on both the sensory and the motor sides of the reflex arc, affecting neither the central nervous system nor the myocardium. By injecting a minute amount of anesthetic into the subarachnoid space, relaxation can be achieved quickly.

Aside from the decreased bleeding that attends this method, there is a decreased cardiac output and a relative type of hypotension that distinguishes this type of anesthesia from that achieved by other techniques. Some consider this harmful, but

we do not, for a good surgical risk patient can easily tolerate a systolic pressure of 60 to 70 mm. of mercury. We often choose this method for surgery in cardiac patients because of the decrease in cardiac work. We seldom see the passive congestion that occurs with inhalation anesthesia, owing to increased intrathoracic pressure, and there is also no accumulation of carbon dioxide. There is no dilated, atonic, gas-filled, and relaxed bowel. The gut is usually hyperactive, so much so that it may even be risky to perform an open anastomosis for fear of spillage of the intestinal contents into the peritoneal cavity. Respiration is quiet, without excess work. There are no accessory muscle movements nor is there respiratory acidosis.

The following are situations in which spinal anesthesia may be the method of choice: husky muscular patients; recent ingestion of food; cesarean sections and prematurity; prior alcoholism or barbiturate addiction; difficult airway problem; controlled hypotension, such as for aortic grafts and portacaval shunts; hepatic, renal, or metabolic diseases; and bowel surgery and intestinal obstruction.

At the University of Pennsylvania, we gave 2500 spinal anesthetics in each of four years—a total of 10,000 patients. Eighty-nine per cent were followed up for four years. The incidence of neurologic sequelae was such that not 1 case of permanent incapacitating progressive paralytic disease was found.

The following components of the syndrome of decreased intracranial pressure were noted after 9277 spinal anesthetics: spinal headache, 11 per cent; ocular difficulties, 0.4 per cent; auditory symptoms, 0.4 per cent. In 89 cases other minor manifestations were observed, such as numbness of feet and toes, perineal numbness, leg numbness, with and without pain, and thigh numbness, with and without pain. We have found that many such symptoms do not occur when proper technique is employed, and especially when smaller gauge needles are used.

## The Use of Muscular Relaxants

Presented by M. JACK FRUMIN, M.D., (Presbyterian Hospital) before the Section on Surgery of the New York Academy of Medicine, January 17, 1956.

There are only two major goals in surgical anesthesia, insensibility and immobility. The chief advantage to be gained from the use of muscular relaxants with a general anesthetic is that the dosage of the latter may be reduced to the point where there are few toxic effects, especially on the circulation. Curariform drugs can take over the job of producing muscular relaxation of any degree, from light to extreme, when administered by any route.

The only disturbance is to the neuromuscular junction itself, where it sets up a blockade. It has little effect on other sites. The chief side effect is apnea. Even a patient who is profoundly relaxed will not be suitable for surgery if the breathing is labored. During the stage of muscle paralysis, endotracheal intubation should be used. It is unwise and dangerous to use these agents in situations in which intubation could not be performed, e.g., congenital or acquired malformations of the head and neck, patients with a tendency to bleed.

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